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     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 13:41:17 ON 05 JUN 2002
L1             0 S CALMODULAIN
L2        110146 S CALMODULIN
L3        342878 S SERINE OR THREONINE
L4         73725 S L3 AND KINASE
L5          6021 S L2 AND L4
L6        422053 S (CELL (A) DEATH) OR APOPTOSIS
L7           391 S L5 AND L6
L8           195 S HUMAN AND L7
L9       1023024 S DOMAIN?
L10          111 S L7 AND L9
L11          345 S DAP(A)KINASE?
L12           72 S L10 AND L11
L13           23 DUP REM L12 (49 DUPLICATES REMOVED)
L14       255022 S CARBOXY(W) TERMINAL OR CARBOXY (W)END OR C-TERMINAL
L15           34 S L10 AND L14
L16           17 DUP REM L15 (17 DUPLICATES REMOVED)
L17        10019 S "DAP"
L18            6 S L16 AND L17
L19         4269 S "ZIP"
L20            2 S L16 AND L19
L21           98 S "DRP-1"
L22            1 S L16 AND L21
                 E KIMCHI A/AU
L23          484 S E3
L24            3 S L16 AND L23
L25            3 DUP REM L24 (0 DUPLICATES REMOVED)
L26            1 S L25 AND DRP##
L27            7 S L23 AND DRP##
L28            2 DUP REM L27 (5 DUPLICATES REMOVED)
L29           81 S L23 AND L17
L30           18 S L29 AND L14
L31            6 DUP REM L30 (12 DUPLICATES REMOVED)
L32           15 S  L16 AND REGULAT?
L33           15 DUP REM L32 (0 DUPLICATES REMOVED)
L34         3919 S "DEATH DOMAIN?"
L35           19 S L15 AND L34
L36            5 DUP REM L35 (14 DUPLICATES REMOVED)
L37        43518 S "DOMINANT NEGATIVE"
L38            5 S L16 AND L37

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* * * * * * * * * * Welcome to STN International * * * * * * * * * *

NEWS	1		Web Page URLs for STN Seminar Schedule - N. America
NEWS	2	Jan 25	BLAST(R) searching in REGISTRY available in STN on the Web
NEWS	3	Jan 29	FSTA has been reloaded and moves to weekly updates
NEWS	4	Feb 01	DKILIT now produced by FIZ Karlsruhe and has a new update frequency
NEWS	5	Feb 19	Access via Tymnet and SprintNet Eliminated Effective 3/31/02
NEWS	6	Mar 08	Gene Names now available in BIOSIS
NEWS	7	Mar 22	TOXLIT no longer available
NEWS	8	Mar 22	TRCTHERMO no longer available
NEWS	9	Mar 28	US Provisional Priorities searched with P in CA/CAplus and USPATFULL
NEWS	10	Mar 28	LIPINSKI/CALC added for property searching in REGISTRY
NEWS	11	Apr 02	PAPERCHEM no longer available on STN. Use PAPERCHEM2 instead.
NEWS	12	Apr 08	"Ask CAS" for self-help around the clock
NEWS	13	Apr 09	BEILSTEIN: Reload and Implementation of a New Subject Area
NEWS	14	Apr 09	ZDB will be removed from STN
NEWS	15	Apr 19	US Patent Applications available in IFICDB, IFIPAT, and IFIUDB
NEWS	16	Apr 22	Records from IP.com available in CAPLUS, HCAPLUS, and ZCAPLUS
NEWS	17	Apr 22	BIOSIS Gene Names now available in TOXCENTER
NEWS	18	Apr 22	Federal Research in Progress (FEDRIP) now available
NEWS	19	May 31	PCTFULL to be reloaded. File temporarily unavailable.
NEWS	20	Jun 03	New e-mail delivery for search results now available

NEWS EXPRESS	February 1 CURRENT WINDOWS VERSION IS V6.0d, CURRENT MACINTOSH VERSION IS V6.0a(ENG) AND V6.0Ja(JP), AND CURRENT DISCOVER FILE IS DATED 05 FEBRUARY 2002
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FILE 'MEDLINE' ENTERED AT 13:41:17 ON 05 JUN 2002

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FILE 'LIFESCI' ENTERED AT 13:41:17 ON 05 JUN 2002
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=> s calmodulain
L1            0 CALMODULAIN

=> s calmodulin
L2       110146 CALMODULIN

=> s serine or threonine
L3       342878 SERINE OR THREONINE

=> s l3 and kinase
L4        73725 L3 AND KINASE

=> s l2 and l4
L5         6021 L2 AND L4

=> s (cell (a) death) or apoptosis
   3 FILES SEARCHED...
L6       422053 (CELL (A) DEATH) OR APOPTOSIS

=> s l5 and l6
L7          391 L5 AND L6

=> s human and l7
L8          195 HUMAN AND L7

=> s domain?
L9      1023024 DOMAIN?

=> s l7 and l9
L10         111 L7 AND L9

=> s DAP(a)kinase?
L11         345 DAP(A) KINASE?

=> s l10 and l11
L12          72 L10 AND L11

=> dup rem l12
PROCESSING COMPLETED FOR L12
L13          23 DUP REM L12 (49 DUPLICATES REMOVED)
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=> d 1-23 ibib ab

L13 ANSWER 1 OF 23 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 2002:89428 SCISEARCH
THE GENUINE ARTICLE: 513UP
TITLE: **DAP kinase** activity is critical for C-2-ceramide-induced **apoptosis** in PC12 cells
AUTHOR: Yamamoto M (Reprint); Hioki T; Ishii T; Nakajima-Iijima S; Uchino S
CORPORATE SOURCE: Mitsubishi Tokyo Pharmaceut Inc, Yokohama Res Ctr, Pharmaceut Discovery Lab, Aoba Ku, 1000 Kamoshida, Yokohama, Kanagawa 2278502, Japan (Reprint); Mitsubishi Tokyo Pharmaceut Inc, Yokohama Res Ctr, Pharmaceut Discovery Lab, Aoba Ku, Yokohama, Kanagawa 2278502, Japan
COUNTRY OF AUTHOR: Japan
SOURCE: EUROPEAN JOURNAL OF BIOCHEMISTRY, (JAN 2002) Vol. 269, No. 1, pp. 139-147.
Publisher: BLACKWELL SCIENCE LTD, P O BOX 88, OSNEY MEAD, OXFORD OX2 0NE, OXON, ENGLAND.
ISSN: 0014-2956.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 41

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Exposure of PC12 cells to C-2-ceramide results in dose-dependent **apoptosis**. Here, we investigate the involvement of death-associated protein (**DAP**) **kinase**, initially identified as a positive mediator of the interferon-gamma-induced **apoptosis** of HeLa cells, in the C-2-ceramide-induced **apoptosis** of PC 12 cells. **DAP kinase** is endogenously expressed in these cells. On exposure of PC 12 cells to 30 muM C-2-ceramide, both the total (assayed in the presence of Ca2+/**calmodulin**) and Ca2+/**calmodulin**-independent (assayed in the presence of EGTA) **DAP kinase** activities were transiently increased 5.0- and 12.2-fold, respectively, at 10 min, and then decreased to 1.7- and 3.4-fold at 90 min. After 10 min exposure to 30 mum C-2-ceramide, the Ca2+/**calmodulin** independent activity/total activity ratio increased from 0.22 to 0.60. These effects were dependent on the C-2-ceramide concentration. C-8-ceramide, another active ceramide analog, also induced **apoptosis** and activated **DAP kinase**, while C-2-dihydroceramide, an inactive ceramide analog, failed to induce **apoptosis** and increase **DAP kinase** activity. Furthermore, transfection studies revealed that overexpression of wild-type **DAP kinase** enhanced the sensitivity to C-2- and C-8-ceramide, while a catalytically inactive **DAP kinase** mutant and a construct containing the death **domain** and C-terminal tail of **DAP kinase**, which act in a dominant-negative manner, rescued cells from C-2-, and C-8-ceramide-induced **apoptosis**. These findings demonstrate that **DAP kinase** is an important component of the apoptotic machinery involved in ceramide-induced **apoptosis**, and that the intrinsic **DAP kinase** activity is critical for ceramide-induced **apoptosis**.

L13 ANSWER 2 OF 23 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2001691904 MEDLINE
DOCUMENT NUMBER: 21601623 PubMed ID: 11579085
TITLE: The pro-apoptotic function of death-associated protein **kinase** is controlled by a unique inhibitory autophosphorylation-based mechanism.
AUTHOR: Shohat G; Spivak-Kroizman T; Cohen O; Bialik S; Shani G;

Berrisi H; Eisenstein M; Kimchi A
CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2001 Dec 14) 276 (50) 47460-7.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200201
ENTRY DATE: Entered STN: 20011213
Last Updated on STN: 20020128
Entered Medline: 20020124

AB Death-associated protein **kinase** is a calcium/**calmodulin** **serine/threonine kinase**, which positively mediates programmed **cell death** in a variety of systems. Here we addressed its mode of regulation and identified a mechanism that restrains its apoptotic function in growing cells and enables its activation during **cell death**. It involves autophosphorylation of Ser(308) within the **calmodulin** (CaM)-regulatory **domain**, which occurs at basal state, in the absence of Ca(2+)/CaM, and is inversely correlated with substrate phosphorylation. This type of phosphorylation takes place in growing cells and is strongly reduced upon their exposure to the apoptotic stimulus of C(6)-ceramide. The substitution of Ser(308) to alanine, which mimics the ceramide-induced dephosphorylation at this site, increases Ca(2+)/CaM-independent substrate phosphorylation as well as binding and overall sensitivity of the **kinase** to CaM. At the cellular level, it strongly enhances the death-promoting activity of the **kinase**. Conversely, mutation to aspartic acid reduces the binding of the protein to CaM and abrogates almost completely the death-promoting function of the protein. These results are consistent with a molecular model in which phosphorylation on Ser(308) stabilizes a locked conformation of the CaM-regulatory **domain** within the catalytic cleft and simultaneously also interferes with CaM binding. We propose that this unique mechanism of auto-inhibition evolved to impose a locking device, which keeps death-associated protein **kinase** silent in healthy cells and ensures its activation only in response to apoptotic signals.

L13 ANSWER 3 OF 23 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 2001:869068 SCISEARCH
THE GENUINE ARTICLE: 485XR
TITLE: Identification of a new form of death-associated protein **kinase** that promotes cell survival
AUTHOR: Jin Y J; Blue E K; Dixon S; Hou L; Wysolmerski R B; Gallagher P J (Reprint)
CORPORATE SOURCE: Indiana Univ, Sch Med, Dept Cellular & Integrated Physiol, 635 Barnhill Dr, Indianapolis, IN 46202 USA (Reprint); Indiana Univ, Sch Med, Dept Cellular & Integrated Physiol, Indianapolis, IN 46202 USA; St Louis Univ, Sch Med, Dept Pathol, St Louis, MO 63104 USA
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (26 OCT 2001) Vol. 276, No. 43, pp. 39667-39678.
Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814 USA.
ISSN: 0021-9258.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 43
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB In this study, two alternatively spliced forms of the mouse death-associated protein **kinase** (DAPK) have been identified and their roles in **apoptosis** examined. The mouse DAPK-alpha sequence is 95% identical to the previously described human DAPK, and it has a **kinase domain** and **calmodulin**-binding region closely related to the 130-150 kDa myosin light chain **kinases**. A beta -residue extension of the carboxyl terminus of DAPK-beta distinguishes it from the human and mouse DAPK-alpha. DAPK phosphorylates at least one substrate in vitro and in vivo, the myosin II regulatory light chain. This phosphorylation occurs preferentially at Ser-19 and is stimulated by calcium and **calmodulin**. The mRNA encoding DAPK is widely distributed and detected in mouse embryos and most adult tissues, although the expression of the encoded 160-kDa DAPK protein is more restricted. Overexpression of DAPK-alpha, the mouse homolog of human DAPK has a negligible effect on tumor necrosis factor (TNF)-induced **apoptosis**. Overexpression of DAPK-beta has a strong cytoprotective effect on TNF-treated cells. Biochemical analysis of TNF-treated cell lines expressing mouse DAPK-beta suggests that the cytoprotective effect of DAPK is mediated through both intrinsic and extrinsic apoptotic signaling pathways and results in the inhibition of cytochrome c release from the mitochondria as well as inhibition of caspase-3 and caspase-9 activity. These results suggest that the mouse DAPK-beta is a negative regulator of TNF-induced **apoptosis**.

L13 ANSWER 4 OF 23 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2001236583 MEDLINE
DOCUMENT NUMBER: 21214579 PubMed ID: 11313923
TITLE: Promoter methylation of **DAP-kinase**: association with advanced stage in non-small cell lung cancer.
AUTHOR: Kim D H; Nelson H H; Wiencke J K; Christiani D C; Wain J C; Mark E J; Kelsey K T
CORPORATE SOURCE: Department of Environmental Health, Harvard School of Public Health, 665 Huntington Avenue, Boston, Massachusetts, MA 02115, USA.
CONTRACT NUMBER: CA06717 (NCI)
CA08357 (NCI)
CA74386 (NCI)
ES/CA 06409 (NIEHS)
SOURCE: ONCOGENE, (2001 Mar 29) 20 (14) 1765-70.
Journal code: ONC; 8711562. ISSN: 0950-9232.
PUB. COUNTRY: England: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200105
ENTRY DATE: Entered STN: 20010517
Last Updated on STN: 20010517
Entered Medline: 20010503

AB Death associated protein (**DAP**)-**kinase** is a 16 kDa **calmodulin**-dependent **serine/threonine kinase** that carries a death **domain** at its C-terminus. **DAP-kinase** functions as a positive mediator of **apoptosis** that is induced by interferon-gamma. Recent studies suggest that **DAP-kinase** is involved in tumor metastasis and that it can be inactivated by methylation of CpG islands in the promoter region of the gene in some human tumors. However, little is known about the factors that are associated with the occurrence of **DAP-kinase** promoter methylation. We investigated both the possible associations of tobacco carcinogen and asbestos exposure with **DAP-kinase** promoter methylation, and the demographic and clinical factors associated with **DAP-kinase** promoter

methylation in non-small cell lung cancer (NSCLC). One hundred and eighty-five patients diagnosed with NSCLC undergoing surgical resection from June, 1992 through December, 1996 at Massachusetts General Hospital participated in this study. Methylation-Specific PCR (MSP), performed using fresh-frozen tissue, was used to determine the methylation status of the promoter region of the **DAP-kinase** gene. Forty-seven (25%) of 185 tumors showed **DAP-kinase** promoter methylation. There was a significant association between methylation and an advanced pathologic stage (P=0.003, Fisher's exact test). Methylation of the **DAP-kinase** promoter was also associated with an increase in tumor size (P=0.009, Fisher's exact test) and lymph node involvement (P=0.04). No association was found between promoter methylation of **DAP-kinase** and k-ras or p53 mutation. In addition there was no association with a history of exposure to tobacco or asbestos. Controlling for age, sex, and histology, the odds ratios describing the association of **DAP-kinase** hypermethylation with stage were 2.70 (1.13--6.45), 3.11 (1.37--7.08) and 7.77 (1.21--50.03) in stages II, III and IV, respectively. Stage I cases with **DAP-kinase** promoter methylation had worse overall survival, but with the small sample size and limited follow-up this did not reach statistical significance. Our findings suggest that methylation of the promoter region of the **DAP-kinase** gene is not associated with exposure to tobacco or asbestos. However, they strongly suggest that **DAP-kinase** may be important in the progression of non-small cell lung cancer from early to late stage disease.

L13 ANSWER 5 OF 23 MEDLINE
ACCESSION NUMBER: 2002071410 MEDLINE
DOCUMENT NUMBER: 21656623 PubMed ID: 11797395
TITLE: Hypermethylation of **DAP-kinase** gene CpG Island in malignant lymphoma with B-cell phenotype.
AUTHOR: Nakatsuka S; Takakuwa T; Aozasa K
CORPORATE SOURCE: Department of Pathology, Osaka University Graduate School of Medicine, Suita 565-0871.
SOURCE: RINSHO BYORI. JAPANESE JOURNAL OF CLINICAL PATHOLOGY, (2001 Dec) 49 (12) 1242-7. Ref: 17
Journal code: 2984781R. ISSN: 0047-1860.
PUB. COUNTRY: Japan
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: Japanese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200203
ENTRY DATE: Entered STN: 20020125
Last Updated on STN: 20020311
Entered Medline: 20020308

AB Death-associated protein-**kinase**(**DAP-Kinase**) is a pro-apoptotic **serine/threonine kinase** with a death **domain**, which is involved in **apoptosis** induced by interferon-gamma, tumor necrosis factor-alpha, and Fas ligand. Epigenetic down-regulation of **DAP-Kinase** gene expression by hypermethylation of its promoter region was reported in certain kinds of malignancies. Previous patho-epidemiological studies indicated that thyroid lymphoma(TL) evolves among active lymphoid cells in chronic lymphocytic thyroiditis(CLTH). With the use of methylation specific polymerase chain reaction, methylation status of **DAP-Kinase** CpG island was examined in thyroid lesions of 19 cases with TL and 9 with CLTH. Frequency of methylation was higher in TL cases(16 of 19, 84.2%) than in CLTH cases(2 of 9, 22.2%) ($p < 0.01$). DNA extracted from peripheral blood leukocytes from TL and CLTH cases never showed

methylation, indicating that the methylation occurred somatically in lesional lymphocytes in the thyroid. We also examined the methylation status of **DAP-kinase** gene in 16 cases of T-cell malignancies including eight adult T-cell leukemia/lymphoma and 24 NK/T-cell, 34 B-cell, and two immunophenotypically undetermined lymphomas. Frequency of methylation was higher in B-cell(27 of 34, 79.4%) than in T-cell malignancies(eight of 16, 50%) ($p < 0.05$). Fifteen of 24(62.5%) NK/T-cell lymphomas showed DNA methylation. Hematopoietic cell lines with a methylated gene were resistant to **apoptosis**. Treatment of the cells with a demethylating agent restored apoptotic **cell death** in one B-cell lymphoma cell line with DNA methylation. Our results suggested that suppression of **DAP-Kinase** expression by DNA methylation might play a role in the development of B-cell malignancies.

L13 ANSWER 6 OF 23 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 2001216755 MEDLINE
DOCUMENT NUMBER: 21153208 PubMed ID: 11230133
TITLE: Autophosphorylation restrains the apoptotic activity of DRP-1 **kinase** by controlling dimerization and **calmodulin** binding.
AUTHOR: Shani G; Henis-Korenblit S; Jona G; Gileadi O; Eisenstein M; Ziv T; Admon A; Kimchi A
CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel.
SOURCE: EMBO JOURNAL, (2001 Mar 1) 20 (5) 1099-113.
Journal code: 8208664. ISSN: 0261-4189.
PUB. COUNTRY: England: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200104
ENTRY DATE: Entered STN: 20010425
Last Updated on STN: 20020420
Entered Medline: 20010419

AB DRP-1 is a pro-apoptotic Ca2+/**calmodulin** (CaM)-regulated **serine/threonine kinase**, recently isolated as a novel member of the **DAP-kinase** family of proteins. It contains a short extra-catalytic tail required for homodimerization. Here we identify a novel regulatory mechanism that controls its pro-apoptotic functions. It comprises a single autophosphorylation event mapped to Ser308 within the CaM regulatory **domain**. A negative charge at this site reduces both the binding to CaM and the formation of DRP-1 homodimers. Conversely, the dephosphorylation of Ser308, which takes place in response to activated Fas or tumour necrosis factor-alpha death receptors, increases the formation of DRP-1 dimers, facilitates the binding to CaM and activates the pro-apoptotic effects of the protein. Thus, the process of enzyme activation is controlled by two unlocking steps that must work in concert, i.e. dephosphorylation, which probably weakens the electrostatic interactions between the CaM regulatory **domain** and the catalytic cleft, and homodimerization. This mechanism of negative autophosphorylation provides a safety barrier that restrains the killing effects of DRP-1, and a target for efficient activation of the **kinase** by various apoptotic stimuli.

L13 ANSWER 7 OF 23 MEDLINE
ACCESSION NUMBER: 2001537809 MEDLINE
DOCUMENT NUMBER: 21457157 PubMed ID: 11573098
TITLE: Crystal structures of the catalytic **domain** of human protein **kinase** associated with **apoptosis** and tumor suppression.
COMMENT: Comment in: Nat Struct Biol. 2001 Oct;8(10):824-6

AUTHOR: Tereshko V; Teplova M; Brunzelle J; Watterson D M; Egli M
CORPORATE SOURCE: Department of Biological Sciences, Vanderbilt University, Nashville, Tennessee 37235, USA.
SOURCE: NATURE STRUCTURAL BIOLOGY, (2001 Oct) 8 (10) 899-907. Journal code: B98; 9421566. ISSN: 1072-8368.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: PDB-1IG1; PDB-1JKK; PDB-1JKL; PDB-1JKS; PDB-1JKT
ENTRY MONTH: 200110
ENTRY DATE: Entered STN: 20011008
Last Updated on STN: 20011022
Entered Medline: 20011018

AB We have determined X-ray crystal structures with up to 1.5 A resolution of the catalytic **domain** of death-associated protein **kinase** (DAPK), the first described member of a novel family of pro-apoptotic and tumor-suppressive **serine/threonine kinases**. The geometry of the active site was studied in the apo form, in a complex with nonhydrolyzable AMPPnP and in a ternary complex consisting of **kinase**, AMPPnP and either Mg2+ or Mn2+. The structures revealed a previously undescribed water-mediated stabilization of the interaction between the lysine that is conserved in protein **kinases** and the beta- and gamma-phosphates of ATP, as well as conformational changes at the active site upon ion binding. Comparison between these structures and nucleotide triphosphate complexes of several other **kinases** disclosed a number of unique features of the DAPK catalytic **domain** , among which is a highly ordered basic loop in the N-terminal **domain** that may participate in enzyme regulation.

L13 ANSWER 8 OF 23 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2001349009 EMBASE
TITLE: A **cell death**-promoting **kinase**
.
AUTHOR: Kimchi A.
CORPORATE SOURCE: A. Kimchi, Department of Molecular Genstics, Weizmann Institute of Science, Rehovot 76100, Israel. adi.kimchi@weizmann.ac.il
SOURCE: Nature Structural Biology, (2001) 8/10 (824-826). Refs: 22
ISSN: 1072-8368 CODEN: NSBIEW
COUNTRY: United States
DOCUMENT TYPE: Journal; (Short Survey)
FILE SEGMENT: 016 Cancer
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Death-associated protein **kinase** (**DAP-kinase**; DAPk) has been implicated in programmed **cell death** and tumor suppression. The recently solved crystal structure of the catalytic **domain** of human **DAP-kinase** reveals interesting 'fingerprint' regions that may be functionally important.

L13 ANSWER 9 OF 23 MEDLINE
ACCESSION NUMBER: 2001169641 MEDLINE
DOCUMENT NUMBER: 21167344 PubMed ID: 11268041
TITLE: The **DAP kinase** family of pro-apoptotic proteins: novel players in the apoptotic game.
AUTHOR: Kogel D; Prehn J H; Scheidtmann K H
CORPORATE SOURCE: Interdisciplinary Center for Clinical Research (IZKF), University of Munster, Germany.. koegel@uni-muenster.de
SOURCE: BIOESSAYS, (2001 Apr) 23 (4) 352-8. Ref: 47

Journal code: 9YY; 8510851. ISSN: 0265-9247.
PUB. COUNTRY: England: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200105
ENTRY DATE: Entered STN: 20010604
Last Updated on STN: 20010604
Entered Medline: 20010531

AB The DAP (Death Associated Protein) **kinase** family is a novel subfamily of pro-apoptotic **serine/threonine kinases**. All five **DAP kinase** family members identified to date are ubiquitously expressed in various tissues and are capable of inducing **apoptosis**. The sequence homology of the five **kinases** is largely restricted to the N-terminal **kinase domain**. In contrast, the adjacent C-terminal regions are very diverse and link individual family members to specific signal transduction pathways. There is increasing evidence that **DAP kinase** family members are involved in both extrinsic and intrinsic pathways of **apoptosis** and may play a role in tumor progression. This review will focus on structural composition and subcellular localization of **DAP kinase** family members and on signal transduction pathways leading to their activation. Potential mechanisms of **DAP kinase** family-mediated **apoptosis** will be discussed. BioEssays 23:352-358, 2001. Copyright 2001 John Wiley & Sons, Inc.

L13 ANSWER 10 OF 23 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 2001:624438 SCISEARCH
THE GENUINE ARTICLE: 459MQ
TITLE: A **serine/threonine kinase** which causes **apoptosis**-like **cell death** interacts with a calcineurin B-like protein capable of binding Na+/H+ exchanger
AUTHOR: Matsumoto M; Miyake Y; Nagita M; Inoue H; Shitakubo D; Takemoto K; Ohtsuka C; Murakami H; Nakamura N; Kanazawa H (Reprint)
CORPORATE SOURCE: Osaka Univ, Grad Sch Sci, Dept Biol Sci, Machikaneyama Cho 1-16, Osaka 5600043, Japan (Reprint); Osaka Univ, Grad Sch Sci, Dept Biol Sci, Osaka 5600043, Japan; Okayama Univ, Fac Engn, Dept Biotechnol, Okayama, Japan
COUNTRY OF AUTHOR: Japan
SOURCE: JOURNAL OF BIOCHEMISTRY, (AUG 2001) Vol. 130, No. 2, pp. 217-225.
Publisher: JAPANESE BIOCHEMICAL SOC, ISHIKAWA BLDG-3F, 25-16 HONGO-5-CHOME, BUNKYO-KU, TOKYO, 113, JAPAN.
ISSN: 0021-924X.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 45
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB We surveyed proteins capable of binding to the cytoplasmic **domain** of Na+/H+ exchanger (NHE)1 in a rat brain cDNA library with the yeast two-hybrid system. One clone obtained coded for a protein reported previously as a human calcineurin homologous protein (CHP). Since CHP is homologous to the regulatory subunit B of calcineurin, we expected a possible interacting partner of CHP like the catalytic subunit of calcineurin (calcineurin A), and surveyed this putative partner again with the yeast two-hybrid system. A clone thus obtained coded for a **kinase**, which is basically the same as that reported for human DRAK2. Overexpression of the rat homologue of DRAK2 caused

apoptosis-like **cell death** of NIH3T3 cells, which was dependent on the **kinase** activity, confirming the previous result for DRAK2. The purified CHP and rat DRAK2 proteins synthesized in Escherichia coli could bind in vitro. CHP and rat DRAK2 expressed in COS-7 cells were found to be localized in the Golgi apparatus and nucleus, respectively. Some of them was also found in the membrane peripheral region. When they were coexpressed in the same cells, most of CHP moved to the nucleus where rat DRAK2 is located, suggesting in vivo interaction of these proteins. However, minor but significant fractions of both proteins were also found in the membrane peripheral region. Rat DRAK2 is expressed highly in thymus, spleen, and testis, where the **apoptosis** plays an important role in physiology.

L13 ANSWER 11 OF 23 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 2001434353 MEDLINE
DOCUMENT NUMBER: 21214809 PubMed ID: 11313698
TITLE: **DAP-kinase**: from functional gene cloning to establishment of its role in **apoptosis** and cancer.
AUTHOR: Cohen O; Kimchi A
CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel.
SOURCE: CELL DEATH AND DIFFERENTIATION, (2001 Jan) 8 (1) 6-15. Ref: 39
Journal code: C7U; 9437445. ISSN: 1350-9047.
PUB. COUNTRY: England: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010806
Last Updated on STN: 20010806
Entered Medline: 20010802

AB **DAP-kinase** is a pro-apoptotic Ca(2+) **calmodulin**-regulated **serine/threonine kinase** that participates in a wide array of apoptotic systems initiated by interferon-gamma, TNF-alpha, activated Fas, and detachment from extracellular matrix. It was isolated by an unbiased functional approach to gene cloning aimed at hitting central mediators of the apoptotic process. This 160 Kd protein **kinase** is localized to actin microfilaments and carries interesting modules such as ankyrin repeats and the death **domain**. The death promoting effects of **DAP-kinase** depend on its intact catalytic activity, the correct intracellular localization, and on the presence of the death **domain**. A few mechanisms restrain the killing effects of the protein in healthy cells. The enzyme's active site is negatively controlled by an adjacent CaM regulatory **domain** whose effect is relieved by binding to Ca(2+)-activated **calmodulin**. A second mode of autoinhibition engages the **serine**-rich C-terminal tail, spanning the last 17 amino acids of the protein. A link between **DAP-kinase** and cancer has been established. It was found that the mRNA and protein expression is frequently lost in various human cancer cell lines. Analysis of the methylation status of **DAP-kinase**'s 5' UTR in DNA extracted from fresh tumor samples, showed high incidence of hypermethylation in several human carcinomas and B cell malignancies. The anti-tumorigenic effect of **DAP-kinase** was also studied experimentally in mouse model systems where the re-introduction of **DAP-kinase** into highly metastatic mouse lung carcinoma cells who had lost the protein, strongly reduced their metastatic capacity. Thus, it appears that loss of **DAP-**

kinase confers a selective advantage to cancer cells and may play a causative role in tumor progression. A few novel **kinases** sharing high homology in their catalytic **domains** with **DAP-kinase** have been recently identified constituting altogether a novel family of death promoting **serine/threonine kinases**.

L13 ANSWER 12 OF 23 MEDLINE
ACCESSION NUMBER: 2001042818 MEDLINE
DOCUMENT NUMBER: 20541072 PubMed ID: 11092525
TITLE: Role of hypermethylation of **DAP-kinase** CpG island in the development of thyroid lymphoma.
AUTHOR: Nakatsuka S; Takakuwa T; Tomita Y; Miwa H; Matsuzuka F; Aozasa K
CORPORATE SOURCE: Department of Patholog, Osaka University Graduate School of Medicine, Japan.
SOURCE: LABORATORY INVESTIGATION, (2000 Nov) 80 (11) 1651-5. Journal code: KZ4. ISSN: 0023-6837.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200012
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001207

AB Death-associated protein-**kinase** (**DAP-Kinase**) is a **serine/threonine kinase** with a death **domain** that is involved in **apoptosis** induced by interferon-gamma, TNF-alpha, and Fas ligand. Epigenetic down-regulation of **DAP-Kinase** gene expression by hypermethylation of its promoter region was reported in B-cell malignancies. Previous pathoepidemiologic studies indicated that thyroid lymphoma (TL) evolves among active lymphoid cells in chronic lymphocytic thyroiditis (CLTH). With use of methylation-specific polymerase chain reaction, the methylation status of **DAP-Kinase** CpG island was examined in thyroid lesions of 19 cases with TL and 9 with CLTH. The frequency of methylation was higher in TL cases (16 of 19, 84.2%) than in CLTH cases (2 of 9, 22.2%) ($p < 0.01$). DNA extracted from peripheral blood leukocytes from TL and CLTH cases never showed methylation, indicating that the methylation occurred somatically in the lesional lymphocytes in thyroid. These findings suggested that methylation of the **DAP-Kinase** promoter region might be involved in the development of TL from CLTH.

L13 ANSWER 13 OF 23 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 2000144081 MEDLINE
DOCUMENT NUMBER: 20144081 PubMed ID: 10677501
TITLE: A functional genetic screen identifies regions at the C-terminal tail and death-**domain** of death-associated protein **kinase** that are critical for its proapoptotic activity.
AUTHOR: Raveh T; Berissi H; Eisenstein M; Spivak T; Kimchi A
CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel.
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (2000 Feb 15) 97 (4) 1572-7. Journal code: PV3; 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 200003
ENTRY DATE: Entered STN: 20000330
Last Updated on STN: 20000330
Entered Medline: 20000323

AB Death-associated protein **kinase** (**DAP-kinase**) is a Ca(+2)/**calmodulin**-regulated **serine/threonine kinase** with a multidomain structure that participates in **apoptosis** induced by a variety of signals. To identify regions in this protein that are critical for its proapoptotic activity, we performed a genetic screen on the basis of functional selection of short **DAP-kinase**-derived fragments that could protect cells from **apoptosis** by acting in a dominant-negative manner. We expressed a library of randomly fragmented **DAP-kinase** cDNA in HeLa cells and treated these cells with IFN-gamma to induce **apoptosis**. Functional cDNA fragments were recovered from cells that survived the selection, and those in the sense orientation were examined further in a secondary screen for their ability to protect cells from **DAP-kinase**-dependent tumor necrosis factor-alpha-induced **apoptosis**. We isolated four biologically active peptides that mapped to the ankyrin repeats, the "linker" region, the death **domain**, and the C-terminal tail of **DAP-kinase**. Molecular modeling of the complete death **domain** provided a structural basis for the function of the death-**domain**-derived fragment by suggesting that the protective fragment constitutes a distinct substructure. The last fragment, spanning the C-terminal **serine**-rich tail, defined a new regulatory region. Ectopic expression of the tail peptide (17 amino acids) inhibited the function of **DAP-kinase**, whereas removal of this region from the complete protein caused enhancement of the killing activity, indicating that the C-terminal tail normally plays a negative regulatory role. Altogether, this unbiased screen highlighted functionally important regions in the protein and revealed an additional level of regulation of **DAP-kinase** apoptotic function that does not affect the catalytic activity.

L13 ANSWER 14 OF 23 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 2000094983 MEDLINE
DOCUMENT NUMBER: 20094983 PubMed ID: 10629061
TITLE: Death-associated protein **kinase**-related protein 1, a novel **serine/threonine kinase** involved in **apoptosis**.
AUTHOR: Inbal B; Shani G; Cohen O; Kissil J L; Kimchi A
CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel.
SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (2000 Feb) 20 (3) 1044-54. Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 20000229
Last Updated on STN: 20020420
Entered Medline: 20000214

AB In this study we describe the identification and structure-function analysis of a novel death-associated protein (**DAP**) **kinase**-related protein, DRP-1. DRP-1 is a 42-kDa Ca(2+)/**calmodulin** (CaM)-regulated **serine threonine kinase** which shows high degree of homology to **DAP kinase**. The region of homology spans the catalytic **domain** and the CaM-regulatory region, whereas the remaining C-terminal part of the protein differs completely from **DAP kinase** and

displays no homology to any known protein. The catalytic **domain** is also homologous to the recently identified ZIP **kinase** and to a lesser extent to the catalytic **domains** of DRAK1 and -2. Thus, **DAP kinase** DRP-1, ZIP **kinase**, and DRAK1/2 together form a novel subfamily of **serine/threonine kinases**. DRP-1 is localized to the cytoplasm, as shown by immunostaining and cellular fractionation assays. It binds to CaM, undergoes autophosphorylation, and phosphorylates an exogenous substrate, the myosin light chain, in a Ca(2+)/CaM-dependent manner. The truncated protein, deleted of the CaM-regulatory **domain**, was converted into a constitutively active **kinase**. Ectopically expressed DRP-1 induced **apoptosis** in various types of cells. Cell killing by DRP-1 was dependent on two features: the status of the catalytic activity, and the presence of the C-terminal 40 amino acids shown to be required for self-dimerization of the **kinase**. Interestingly, further deletion of the CaM-regulatory region could override the indispensable role of the C-terminal tail in **apoptosis** and generated a "superkiller" mutant. A dominant negative fragment of **DAP kinase** encompassing the death **domain** was found to block **apoptosis** induced by DRP-1. Conversely, a catalytically inactive mutant of DRP-1, which functioned in a dominant negative manner, was significantly less effective in blocking **cell death** induced by **DAP kinase**. Possible functional connections between **DAP kinase** and DRP-1 are discussed.

L13 ANSWER 15 OF 23 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 1999:472355 SCISEARCH
THE GENUINE ARTICLE: 205ZF
TITLE: Death-associated protein **kinase** 2 is a new calcium/**calmodulin**-dependent protein **kinase** that signals **apoptosis** through its catalytic activity
AUTHOR: Kawai T; Nomura F; Hoshino K; Copeland N G; Gilbert D J; Jenkins N A; Akira S (Reprint)
CORPORATE SOURCE: HYOGO MED UNIV, DEPT BIOCHEM, 1-1 MUKOGAWA CHO, NISHINOMIYA, HYOGO 6638501, JAPAN (Reprint); HYOGO MED UNIV, DEPT BIOCHEM, NISHINOMIYA, HYOGO 6638501, JAPAN; NCI, MAMMALIAN GENET LAB, ABL BASIC RES PROGRAM, FREDERICK CANC RES & DEV CTR, FREDERICK, MD 21702; JAPAN SCI & TECHNOL CORP, CREST, TOKYO, JAPAN
COUNTRY OF AUTHOR: JAPAN; USA
SOURCE: ONCOGENE, (10 JUN 1999) Vol. 18, No. 23, pp. 3471-3480. Publisher: STOCKTON PRESS, HOUNDMILLS, BASINGSTOKE RG21 6XS, HAMPSHIRE, ENGLAND.
ISSN: 0950-9232.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 45

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB We have identified and characterized a new calcium/**calmodulin** (Ca2+/CaM) dependent protein **kinase** termed death-associated protein **kinase** 2 (DAPK2) that contains an N-terminal protein **kinase domain** followed by a conserved CaM-binding **domain** with significant homologies to those of **DAP kinase**, a protein **kinase** involved in **apoptosis** , DAPK2 mRNA is expressed abundantly in heart, lung and skeletal muscle. The mapping results indicated that DAPK2 is located in the central region of mouse chromosome 9, bl vitro **kinase** assay revealed that DAPK2 is autophosphorylated and phosphorylates myosin light chain (MLC) as an exogenous substrate. DAPK2 binds directly to CaM and is activated in a Ca2+/CaM-dependent manner. A constitutively active DAPK2 mutant is

generated by removal of the CaM-binding **domain** (Delta CaM). Treatment of agonists that elevate intracellular Ca2+-concentration led to the activation of DAPK2 and transfection studies revealed that DAPK2 is localized in the cytoplasm. Overexpression of DAPK2, but not the **kinase** negative mutant, significantly induced the morphological changes characteristic of **apoptosis**, These results indicate that DAPK2 is an additional member of **DAP kinase** family involved in apoptotic signaling.

L13 ANSWER 16 OF 23 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 2000030159 MEDLINE
DOCUMENT NUMBER: 20030159 PubMed ID: 10561695
TITLE: Developmental changes in distribution of death-associated protein **kinase** mRNAs.
AUTHOR: Yamamoto M; Takahashi H; Nakamura T; Hioki T; Nagayama S; Ooashi N; Sun X; Ishii T; Kudo Y; Nakajima-Iijima S; Kimchi A; Uchino S
CORPORATE SOURCE: Pharmaceuticals Discovery Laboratory, Yokohama Research Center, Mitsubishi Chemical Corporation, Aoba-ku, Yokohama, Japan.
SOURCE: JOURNAL OF NEUROSCIENCE RESEARCH, (1999 Dec 1) 58 (5) 674-83.
Journal code: KAC; 7600111. ISSN: 0360-4012.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200001
ENTRY DATE: Entered STN: 20000114
Last Updated on STN: 20000114
Entered Medline: 20000105

AB Death-associated protein **kinase** (**DAP-kinase**) is Ca(2+)/**calmodulin**-dependent **serine/threonine kinase** that contains ankyrin repeats and the death **domain**. It has been isolated as a positive mediator of interferon-gamma-induced apoptotic **cell death** of HeLa cells. In order to reveal the physiological role of **DAP-kinase**, the tissue distribution and developmental changes in mRNA expression of **DAP-kinase** were investigated by Northern blot and in situ hybridization analyses. **DAP-kinase** mRNA was predominantly expressed in brain and lung. In brain, **DAP-kinase** mRNA had already appeared at embryonic day 13 (E13) and was, thereafter, detected throughout the entire embryonic period. High levels of expression were detected in proliferative and postmitotic regions within cerebral cortex, hippocampus, and cerebellar Purkinje cells. These findings suggest that **DAP-kinase** may play an important role in neurogenesis where a physiological type of **cell death** takes place. The overall expression of **DAP-kinase** mRNA in the brain gradually declined at postnatal stages, and the expression became restricted to hippocampus, in which different expression patterns were observed among rostral, central, and caudal coronal sections, suggesting that **DAP-kinase** may be implicated in some neuronal functions. Furthermore, it was found that the expression of **DAP-kinase** mRNA was increased prior to a certain **cell death** induced by transient forebrain ischemia, indicating a possible relationship between **DAP-kinase** and neuronal **cell death**.

L13 ANSWER 17 OF 23 MEDLINE
ACCESSION NUMBER: 1999148017 MEDLINE
DOCUMENT NUMBER: 99148017 PubMed ID: 10023074

TITLE: Duet is a novel **serine/threonine kinase** with Dbl-Homology (DH) and Pleckstrin-Homology (PH) **domains**.
AUTHOR: Kawai T; Sanjo H; Akira S
CORPORATE SOURCE: Department of Biochemistry, Hyogo College of Medicine, 1-1 Mukogawa-cho, Nishinomiya, Hyogo, 663-8501, Japan.
SOURCE: GENE, (1999 Feb 18) 227 (2) 249-55.
Journal code: FOP; 7706761. ISSN: 0378-1119.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AB011422
ENTRY MONTH: 199904
ENTRY DATE: Entered STN: 19990426
Last Updated on STN: 20000303
Entered Medline: 19990413

AB We show here the identification of Duet, a novel molecule bearing **serine/threonine kinase**, Dbl-Homology (DH), and Pleckstrin-Homology (PH) **domains**. The **kinase domain** of Duet shows a homology to that of **DAP kinase** that is involved in **apoptosis**, and Duet is autophosphorylated by an in-vitro **kinase** assay. The DH- and PH-**domains** are closely related to those of Trio and Kalirin. Trad mRNA is specifically expressed in skeletal muscle. Duet protein was localized to actin-associated cytoskeletal elements. These data suggest a role of Duet in the cytoskeleton-dependent cell function.

L13 ANSWER 18 OF 23 MEDLINE DUPLICATE 8
ACCESSION NUMBER: 1999332304 MEDLINE
DOCUMENT NUMBER: 99332304 PubMed ID: 10402466
TITLE: **DAP-kinase** participates in TNF-alpha- and Fas-induced **apoptosis** and its function requires the death **domain**.
AUTHOR: Cohen O; Inbal B; Kissil J L; Raveh T; Berissi H; Spivak-Kroizaman T; Feinstein E; Kimchi A
CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel.
SOURCE: JOURNAL OF CELL BIOLOGY, (1999 Jul 12) 146 (1) 141-8.
Journal code: HMV; 0375356. ISSN: 0021-9525.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199908
ENTRY DATE: Entered STN: 19990820
Last Updated on STN: 19990820
Entered Medline: 19990809

AB Death-associated protein (**DAP**)-**kinase** is a calcium/**calmodulin** regulated **serine/threonine kinase** that carries ankyrin repeats, a death **domain**, and is localized to the cytoskeleton. Here, we report that this **kinase** is involved in tumor necrosis factor (TNF)-alpha and Fas-induced **apoptosis**. Expression of **DAP-kinase** antisense RNA protected cells from killing by anti-Fas/APO-1 agonistic antibodies. Deletion of the death **domain** abrogated the apoptotic functions of the **kinase**, thus, documenting for the first time the importance of this protein **domain**. Overexpression of a fragment encompassing the death **domain** of **DAP-kinase** acted as a specific dominant negative mutant that protected cells from TNF-alpha, Fas, and FADD/MORT1-induced **cell death**. **DAP-kinase** apoptotic function was blocked by bcl-2 as

well as by crmA and p35 inhibitors of caspases, but not by the dominant negative mutants of FADD/MORT1 or of caspase 8. Thus, it functions downstream to the receptor complex and upstream to other caspases. The multidomain structure of this **serine/threonine kinase**, combined with its involvement in **cell death** induced by several different triggers, place **DAP-kinase** at one of the central molecular pathways leading to **apoptosis**.

L13 ANSWER 19 OF 23 MEDLINE
ACCESSION NUMBER: 1999003259 MEDLINE
DOCUMENT NUMBER: 99003259 PubMed ID: 9786912
TITLE: DRAKs, novel **serine/threonine kinases** related to death-associated protein **kinase** that trigger **apoptosis**.
AUTHOR: Sanjo H; Kawai T; Akira S
CORPORATE SOURCE: Department of Biochemistry, Hyogo College of Medicine, 1-1 Mukogawa-cho, Nishinomiya, Hyogo 663-8501, Japan.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1998 Oct 30) 273 (44) 29066-71.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AB011420; GENBANK-AB011421
ENTRY MONTH: 199812
ENTRY DATE: Entered STN: 19990115
Last Updated on STN: 20020420
Entered Medline: 19981201

AB The present study describes the cloning of two novel **serine/threonine kinases** termed DRAK1 and DRAK2, whose catalytic **domains** are related to that of death-associated protein **kinase**, a **serine/threonine kinase** involved in **apoptosis**. Both DRAKs are composed of the N-terminal catalytic **domain** and the C-terminal **domain** that is responsible for regulation of **kinase** activity. DRAK1 and DRAK2 show 59.7% identity and display ubiquitous expression. An in vitro **kinase** assay revealed that both DRAKs are autophosphorylated and phosphorylate myosin light chain as an exogenous substrate, although the **kinase** activity of DRAK2 is significantly lower than that of DRAK1. Both DRAKs are exclusively localized to the nucleus. Furthermore, overexpression of both DRAKs induces the morphological changes of **apoptosis** in NIH 3T3 cells, suggesting the role of DRAKs in apoptotic signaling.

L13 ANSWER 20 OF 23 MEDLINE
ACCESSION NUMBER: 1998147805 MEDLINE
DOCUMENT NUMBER: 98147805 PubMed ID: 9488481
TITLE: ZIP **kinase**, a novel **serine/threonine kinase** which mediates **apoptosis**.
AUTHOR: Kawai T; Matsumoto M; Takeda K; Sanjo H; Akira S
CORPORATE SOURCE: Department of Biochemistry, Hyogo College of Medicine, Nishinomiya, Japan.
SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (1998 Mar) 18 (3) 1642-51.
Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AB007143; GENBANK-AB007144

ENTRY MONTH: 199803
ENTRY DATE: Entered STN: 19980326
Last Updated on STN: 20020420
Entered Medline: 19980319

AB We have identified a novel **serine/threonine kinase**, designated ZIP **kinase**, which mediates **apoptosis**. ZIP **kinase** contains a leucine zipper structure at its C terminus, in addition to a **kinase domain** at its N terminus. ZIP **kinase** physically binds to ATF4, a member of the activating transcription factor/cyclic AMP-responsive element-binding protein (ATF/CREB) family, through interaction between their leucine zippers. The leucine zipper **domain** is necessary for the homodimerization of ZIP **kinase** as well as for the activation of **kinase**. Immunostaining study showed that ZIP **kinase** localizes in the nuclei. Overexpression of intact ZIP **kinase** but not catalytically inactive **kinase** mutants led to the morphological changes of **apoptosis** in NIH 3T3 cells, suggesting that the **cell death**-inducing activity of ZIP **kinase** depends on its intrinsic **kinase** activity. Interestingly, the catalytic **domain** of ZIP **kinase** is closely related to that of death-associated protein **kinase** (**DAP kinase**), which is a mediator of **apoptosis** induced by gamma interferon. Therefore, both ZIP and **DAP kinases** represent a novel **kinase** family, which mediates **apoptosis** through their catalytic activities.

L13 ANSWER 21 OF 23 MEDLINE DUPLICATE 9
ACCESSION NUMBER: 97224127 MEDLINE
DOCUMENT NUMBER: 97224127 PubMed ID: 9118961
TITLE: **DAP-kinase** is a Ca2+/**calmodulin**-dependent, cytoskeletal-associated protein **kinase**, with **cell death**-inducing functions that depend on its catalytic activity.
AUTHOR: Cohen O; Feinstein E; Kimchi A
CORPORATE SOURCE: Department of Molecular Genetics, The Weizmann Institute of Science, Rehovot, Israel.
SOURCE: EMBO JOURNAL, (1997 Mar 3) 16 (5) 998-1008.
Journal code: EMB; 8208664. ISSN: 0261-4189.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199704
ENTRY DATE: Entered STN: 19970506
Last Updated on STN: 19980206
Entered Medline: 19970422

AB **DAP-kinase** was initially identified as a gene whose anti-sense-mediated reduced expression protected HeLa cells from interferon-gamma-induced programmed **cell death**. It was cloned in our laboratory by a functional gene selection approach. According to its amino acid sequence, this 160 kDa protein was predicted to be a novel type of **calmodulin**-regulated **serine/threonine kinase** which carries ankyrin repeats and the death **domain**. In this work we have shown that the **kinase** was autophosphorylated and capable of phosphorylating an exogenous substrate in a Ca2+/**calmodulin**-dependent manner. We proved that **calmodulin** binds directly to the recombinant **kinase**, and generated a constitutively active **kinase** mutant by the deletion of the **calmodulin**-regulatory **domain**. By immunostaining and biochemical fractionations we demonstrated that the **kinase** is localized to the cytoskeleton, in association with the microfilament

system, and mapped a region within the protein which is responsible for binding to the cytoskeleton. Several assays attributed a **cell death** function to the gene. Ectopic expression of wild-type **DAP-kinase** induced the death of target cells, and the killing property depended strictly on the status of the intrinsic **kinase** activity. Conversely, a catalytically inactive mutant that carried a lysine to alanine substitution within the **kinase domain**, displayed dominant-negative features and protected cells from interferon-gamma-induced **cell death**. **DAP -kinase** is therefore a novel cytoskeletal-associated **cell death serine/threonine kinase** whose activation by Ca2+/**calmodulin** may be linked to the biochemical mechanism underlying the cytoskeletal alterations that occur during **cell death**.

L13 ANSWER 22 OF 23 MEDLINE DUPLICATE 10
ACCESSION NUMBER: 97384865 MEDLINE
DOCUMENT NUMBER: 97384865 PubMed ID: 9242376
TITLE: **DAP-kinase** loss of expression in various carcinoma and B-cell lymphoma cell lines: possible implications for role as tumor suppressor gene.
AUTHOR: Kissil J L; Feinstein E; Cohen O; Jones P A; Tsai Y C; Knowles M A; Eydmann M E; Kimchi A
CORPORATE SOURCE: Department of Molecular Genetics, The Weizmann Institute of Science, Rehovot, Israel.
CONTRACT NUMBER: CA49758 (NCI)
SOURCE: ONCOGENE, (1997 Jul 24) 15 (4) 403-7.
Journal code: ONC; 8711562. ISSN: 0950-9232.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199708
ENTRY DATE: Entered STN: 19970902
Last Updated on STN: 19980206
Entered Medline: 19970821

AB **DAP-kinase** is a novel **calmodulin** dependent **serine/threonine kinase** that carries ankyrin repeats and the death **domain**. It was recently isolated, by a functional selection approach of gene cloning, as a positive mediator of programmed **cell death**. In this study the expression of **DAP-kinase** was examined in the cell lines derived from various human neoplasms. **DAP-kinase** mRNA and protein expression were below the limit of detection in eight out of ten neoplastic derived B-cell lines. In six out of 14 examined bladder carcinoma, in three out of five renal cell carcinoma, and in four out of ten tested breast carcinoma cell lines, the **DAP-kinase** protein levels were below detection limits or lower than 1% compared to the positive cell lines. Interestingly, **DAP-kinase** expression could be restored in some of the negative bladder carcinoma and B-cell lines by treatment of cells with 5'-azadeoxycytidine that causes DNA demethylation. The high frequency of loss of **DAP-kinase** expression in human tumor cell lines, and the occasional involvement of methylation in this process raise the possibility that this novel mediator of **cell death** may function as a tumor suppressor gene.

L13 ANSWER 23 OF 23 MEDLINE DUPLICATE 11
ACCESSION NUMBER: 1998032978 MEDLINE
DOCUMENT NUMBER: 98032978 PubMed ID: 9367156
TITLE: **DAP kinase** links the control of **apoptosis** to metastasis.

AUTHOR: Inbal B; Cohen O; Polak-Charcon S; Kopolovic J; Vadai E; Eisenbach L; Kimchi A
CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot, Israel.
SOURCE: NATURE, (1997 Nov 13) 390 (6656) 180-4.
Journal code: NSC; 0410462. ISSN: 0028-0836.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199711
ENTRY DATE: Entered STN: 19971224
Last Updated on STN: 19971224
Entered Medline: 19971125

AB **DAP kinase** is a new type of calcium/**calmodulin** -dependent enzyme that phosphorylates **serine/threonine** residues on proteins. Its structure contains ankyrin repeats and the 'death' **domain**, and it is associated with the cell cytoskeleton. The gene encoding **DAP kinase** was initially isolated as a positive mediator of **apoptosis** induced by interferon-gamma, by using a strategy of functional cloning. We have now tested whether this gene has tumour-suppressive activity. We found that lung carcinoma clones, characterized by their highly aggressive metastatic behaviour and originating from two independent murine lung tumours, did not express **DAP kinase**, in contrast to their low-metastatic counterparts. Restoration of **DAP kinase** to physiological levels in high-metastatic Lewis carcinoma cells suppressed their ability to form lung metastases after intravenous injection into syngeneic mice, and delayed local tumour growth in a foreign 'microenvironment' Conversely, in vivo selection of rare lung lesions following injection into syngeneic mice of low-metastatic Lewis carcinoma cells or of **DAP kinase** transfectants, was associated with loss of **DAP kinase** expression. In situ TUNEL staining of tumour sections revealed that **DAP kinase** expression from the transgene raised the incidence of **apoptosis** in vivo. **DAP-kinase** transfectants also showed increased sensitivity in vitro to apoptotic stimuli, of the sort encountered by metastasizing cells at different stages of malignancy. We propose that loss of **DAP kinase** expression provides a unique mechanism that links suppression of **apoptosis** to metastasis.

=> d his

(FILE 'HOME' ENTERED AT 13:40:52 ON 05 JUN 2002)

FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS, LIFESCI' ENTERED AT 13:41:17 ON 05 JUN 2002

L1	0	S	CALMODULAIN
L2	110146	S	CALMODULIN
L3	342878	S	SERINE OR THREONINE
L4	73725	S	L3 AND KINASE
L5	6021	S	L2 AND L4
L6	422053	S	(CELL (A) DEATH) OR APOPTOSIS
L7	391	S	L5 AND L6
L8	195	S	HUMAN AND L7
L9	1023024	S	DOMAIN?
L10	111	S	L7 AND L9
L11	345	S	DAP(A)KINASE?
L12	72	S	L10 AND L11
L13	23		DUP REM L12 (49 DUPLICATES REMOVED)

```
=> s carboxy(w) terminal or carboxy (w)end or C-terminal
   3 FILES SEARCHED...
L14     255022 CARBOXY(W) TERMINAL OR CARBOXY (W) END OR C-TERMINAL

=> s l10 and l14
L15         34 L10 AND L14

=> dup rem l15
PROCESSING COMPLETED FOR L15
L16          17 DUP REM L15 (17 DUPLICATES REMOVED)

=> d 1-17 ibib ab

L16  ANSWER 1 OF 17  SCISEARCH  COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER:    2002:89428  SCISEARCH
THE GENUINE ARTICLE: 513UP
TITLE:               DAP kinase activity is critical for
                     C-2-ceramide-induced apoptosis in PC12 cells
AUTHOR:              Yamamoto M (Reprint); Hioki T; Ishii T; Nakajima-Iijima S;
                     Uchino S
CORPORATE SOURCE:    Mitsubishi Tokyo Pharmaceut Inc, Yokohama Res Ctr,
                     Pharmaceut Discovery Lab, Aoba Ku, 1000 Kamoshida,
                     Yokohama, Kanagawa 2278502, Japan (Reprint); Mitsubishi
                     Tokyo Pharmaceut Inc, Yokohama Res Ctr, Pharmaceut
                     Discovery Lab, Aoba Ku, Yokohama, Kanagawa 2278502, Japan
COUNTRY OF AUTHOR:   Japan
SOURCE:              EUROPEAN JOURNAL OF BIOCHEMISTRY, (JAN 2002) Vol. 269, No.
                     1, pp. 139-147.
                     Publisher: BLACKWELL SCIENCE LTD, P O BOX 88, OSNEY MEAD,
                     OXFORD OX2 0NE, OXON, ENGLAND.
                     ISSN: 0014-2956.
DOCUMENT TYPE:       Article; Journal
LANGUAGE:            English
REFERENCE COUNT:     41
                    *ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*
AB       Exposure of PC12 cells to C-2-ceramide results in dose-dependent
     apoptosis. Here, we investigate the involvement of
     death-associated protein (DAP) kinase, initially identified as a
     positive mediator of the interferon-gamma-induced apoptosis of
     HeLa cells, in the C-2-ceramide-induced apoptosis of PC 12
     cells. DAP kinase is endogenously expressed in these cells. On
     exposure of PC 12 cells to 30 muM C-2-ceramide, both the total (assayed in
     the presence of Ca2+/calmodulin) and Ca2+/calmodulin
     -independent (assayed in the presence of EGTA) DAP kinase
     activities were transiently increased 5.0- and 12.2-fold, respectively, at
     10 min, and then decreased to 1.7- and 3.4-fold at 90 min. After 10 min
     exposure to 30 mum C-2-ceramide, the Ca2+/calmodulin independent
     activity/total activity ratio increased from 0.22 to 0.60. These effects
     were dependent on the C-2-ceramide concentration. C-8-ceramide, another
     active ceramide analog, also induced apoptosis and activated DAP
     kinase, while C-2-dihydroceramide, an inactive ceramide analog,
     failed to induce apoptosis and increase DAP kinase
     activity. Furthermore, transfection studies revealed that overexpression
     of wild-type DAP kinase enhanced the sensitivity to C-2- and
     C-8-ceramide, while a catalytically inactive DAP kinase mutant
     and a construct containing the death domain and C-
     terminal tail of DAP kinase, which act in a
     dominant-negative manner, rescued cells from C-2-, and
     C-8-ceramide-induced apoptosis. These findings demonstrate that
     DAP kinase is an important component of the apoptotic machinery
     involved in ceramide-induced apoptosis, and that the intrinsic
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DAP **kinase** activity is critical for ceramide-induced **apoptosis**.

L16 ANSWER 2 OF 17 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:43345 HCAPLUS
DOCUMENT NUMBER: 136:319709
TITLE: Transcriptional profiling reveals global defects in energy metabolism, lipoprotein, and bile acid synthesis and transport with reversal by leptin treatment in Ob/ob mouse liver
AUTHOR(S): Liang, Chien-Ping; Tall, Alan R.
CORPORATE SOURCE: Division of Molecular Medicine, Department of Medicine, Columbia University, New York, NY, 10032, USA
SOURCE: Journal of Biological Chemistry (2001), 276(52), 49066-49076
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Leptin, a hormone secreted by adipose tissue, has been shown to have a major influence on hepatic lipid and lipoprotein metab. To characterize changes in lipid and lipoprotein gene expression in mouse liver, suppression subtractive hybridization and cDNA microarray anal. were used to identify mRNAs differentially expressed after leptin treatment of ob/ob mice. Ob/ob mice showed a profound decrease in mRNAs encoding genes controlling bile acid synthesis and transport as well as a variety of apolipoprotein genes and hepatic lipase with reversal upon leptin administration, suggesting that leptin coordinately regulates high d. lipoprotein and bile salt metab. Leptin administration also resulted in decreased expression of genes involved in fatty acid and cholesterol synthesis, glycolysis, gluconeogenesis, and urea synthesis, and increased expression of genes mediating fatty acid oxidn., ATP synthesis, and oxidant defenses. The changes in mRNA expression are consistent with a switch in energy metab. from glucose utilization and fatty acid synthesis to fatty acid oxidn. and increased respiration. The latter changes may produce oxidant stress, explaining the unexpected finding that leptin induces a battery of genes involved in antioxidant defenses. Expression cluster anal. revealed responses of several sets of genes that were kinetically linked. Thus, the mRNA levels of genes involved in fatty acid and cholesterol synthesis are rapidly (<1 h) repressed by leptin administration, in assocn. with an acute decrease in plasma insulin levels and decreased sterol regulator element-binding protein-1 expression. In contrast, genes participating in fatty acid oxidn. and ketogenesis were induced more slowly (24 h), following an increase in expression of their common regulatory factor, peroxisome proliferator-activated receptor .alpha.. However, the regulation of genes involved in high d. lipoprotein and bile salt metab. shows complex kinetics and is likely to be mediated by novel transcription factors.
REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 3 OF 17 MEDLINE
ACCESSION NUMBER: 2001169641 MEDLINE
DOCUMENT NUMBER: 21167344 PubMed ID: 11268041
TITLE: The DAP **kinase** family of pro-apoptotic proteins: novel players in the apoptotic game.
AUTHOR: Kogel D; Prehn J H; Scheidtmann K H
CORPORATE SOURCE: Interdisciplinary Center for Clinical Research (IZKF), University of Munster, Germany.. koegel@uni-muenster.de
SOURCE: BIOESSAYS, (2001 Apr) 23 (4) 352-8. Ref: 47

Journal code: 9YY; 8510851. ISSN: 0265-9247.
PUB. COUNTRY: England: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200105
ENTRY DATE: Entered STN: 20010604
Last Updated on STN: 20010604
Entered Medline: 20010531

AB The DAP (Death Associated Protein) **kinase** family is a novel subfamily of pro-apoptotic **serine/threonine kinases**. All five DAP **kinase** family members identified to date are ubiquitously expressed in various tissues and are capable of inducing **apoptosis**. The sequence homology of the five **kinases** is largely restricted to the N-terminal **kinase domain**. In contrast, the adjacent **C-terminal** regions are very diverse and link individual family members to specific signal transduction pathways. There is increasing evidence that DAP **kinase** family members are involved in both extrinsic and intrinsic pathways of **apoptosis** and may play a role in tumor progression. This review will focus on structural composition and subcellular localization of DAP **kinase** family members and on signal transduction pathways leading to their activation. Potential mechanisms of DAP **kinase** family-mediated **apoptosis** will be discussed. BioEssays 23:352-358, 2001. Copyright 2001 John Wiley & Sons, Inc.

L16 ANSWER 4 OF 17 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:775265 HCAPLUS
DOCUMENT NUMBER: 136:132090
TITLE: Investigation of differentially expressed genes during the development of mouse cerebellum
AUTHOR(S): Kagami, Yoshihiro; Furuichi, Teiichi
CORPORATE SOURCE: Laboratory for Molecular Neurogenesis, Brain Science Institute, RIKEN, Wako, 351-0198, Japan
SOURCE: Gene Expression Patterns (2001), 1(1), 39-59
CODEN: GEPEAD; ISSN: 1567-133X
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Before the discovery of DNA microarray and DNA chip technol., the expression of only a small no. of genes could be analyzed at a time. Currently, such technol. allows us the simultaneous anal. of a large no. of genes to systematically monitor their expression patterns that may be assocd. with various biol. phenomena. We utilized the Affymetrix GeneChip Mu11K to analyze the gene expression profile in developing mouse cerebellum to assist in the understanding of the genetic basis of cerebellar development in mice. Our anal. showed 81.6% (10.321/12.654) of the genes represented on the GeneChip were expressed in the postnatal cerebellum, and among those, 8.7% (897/10.321) were differentially expressed with more than a two-fold change in their max. and min. expression levels during the developmental time course. Further anal. of the differentially expressed genes that were clustered in terms of their expression patterns and the function of their encoded products revealed an aspect of the genetic foundation that lies beneath the cellular events and neural network formation that takes place during the development of the mouse cerebellum.

REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 5 OF 17 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2001434353 MEDLINE
DOCUMENT NUMBER: 21214809 PubMed ID: 11313698
TITLE: DAP-**kinase**: from functional gene cloning to establishment of its role in **apoptosis** and cancer.
AUTHOR: Cohen O; Kimchi A
CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel.
SOURCE: CELL DEATH AND DIFFERENTIATION, (2001 Jan) 8 (1) 6-15.
Ref: 39
Journal code: C7U; 9437445. ISSN: 1350-9047.
PUB. COUNTRY: England: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010806
Last Updated on STN: 20010806
Entered Medline: 20010802

AB DAP-**kinase** is a pro-apoptotic Ca(2+) **calmodulin**-regulated **serine/threonine kinase** that participates in a wide array of apoptotic systems initiated by interferon-gamma, TNF-alpha, activated Fas, and detachment from extracellular matrix. It was isolated by an unbiased functional approach to gene cloning aimed at hitting central mediators of the apoptotic process. This 160 Kd protein **kinase** is localized to actin microfilaments and carries interesting modules such as ankyrin repeats and the death **domain**. The death promoting effects of DAP-**kinase** depend on its intact catalytic activity, the correct intracellular localization, and on the presence of the death **domain**. A few mechanisms restrain the killing effects of the protein in healthy cells. The enzyme's active site is negatively controlled by an adjacent CaM regulatory **domain** whose effect is relieved by binding to Ca(2+)-activated **calmodulin**. A second mode of autoinhibition engages the **serine**-rich **C-terminal** tail, spanning the last 17 amino acids of the protein. A link between DAP-**kinase** and cancer has been established. It was found that the mRNA and protein expression is frequently lost in various human cancer cell lines. Analysis of the methylation status of DAP-**kinase**'s 5' UTR in DNA extracted from fresh tumor samples, showed high incidence of hypermethylation in several human carcinomas and B cell malignancies. The anti-tumorigenic effect of DAP-**kinase** was also studied experimentally in mouse model systems where the re-introduction of DAP-**kinase** into highly metastatic mouse lung carcinoma cells who had lost the protein, strongly reduced their metastatic capacity. Thus, it appears that loss of DAP-**kinase** confers a selective advantage to cancer cells and may play a causative role in tumor progression. A few novel **kinases** sharing high homology in their catalytic **domains** with DAP-**kinase** have been recently identified constituting altogether a novel family of death promoting **serine/threonine kinases**.

L16 ANSWER 6 OF 17 MEDLINE
ACCESSION NUMBER: 2000187596 MEDLINE
DOCUMENT NUMBER: 20187596 PubMed ID: 10722720
TITLE: Activation of MST/Krs and c-Jun N-terminal **kinases** by different signaling pathways during cytotrienin A-induced **apoptosis**.
AUTHOR: Watabe M; Kakeya H; Onose R; Osada H

CORPORATE SOURCE: Antibiotics Laboratory, RIKEN, 2-1 Hirosawa, Wako-shi, Saitama 351-0198, Japan.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2000 Mar 24) 275 (12) 8766-71.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200004
ENTRY DATE: Entered STN: 20000505
Last Updated on STN: 20020420
Entered Medline: 20000427

AB We found that antitumor drugs such as cytotrienin A, camptothecin, taxol, and 5-fluorouracil induced the activation of a 36-kDa protein **kinase** (p36 myelin basic protein (MBP) **kinase**) during **apoptosis** in human promyelocytic leukemia HL-60 cells. This p36 MBP **kinase**, which phosphorylates MBP in an in-gel **kinase** assay, results from the caspase-3-mediated proteolytic cleavage of MST/Krs protein, a mammalian Ste20-like **serine/threonine** **kinase**. Herein the correlation between cytotrienin A-induced **apoptosis** and the activation of MST/Krs proteins was examined in human tumor cell lines, including leukemia-, lung-, epidermoid-, cervix-, stomach-, and brain-derived cell lines. In cytotrienin A-sensitive cell lines, we observed a strong activation of p36 MBP **kinase** by cleavage of the **C-terminal** regulatory **domain** of full-length MST/Krs proteins by caspase-3. When the **kinase** -inactive mutant form of MST/Krs protein was overexpressed in cytotrienin A-sensitive HL-60 cells, the cytotrienin A-induced **apoptosis** was partially inhibited. Because cytotrienin A also activated c-Jun N-terminal **kinase**, we examined the effect of the expression of dominant negative c-Jun on cytotrienin A-induced **apoptosis**. The expression of dominant negative c-Jun also partially inhibited cytotrienin A-induced **apoptosis**. Furthermore, coexpression of **kinase** -inactive MST/Krs protein and dominant negative c-Jun completely suppressed cytotrienin A-induced **apoptosis**. These findings suggest that the proteolytic activation of MST/Krs and c-Jun N-terminal **kinase** activation are involved in cytotrienin A-induced **apoptosis** in human tumor cell lines.

L16 ANSWER 7 OF 17 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2000144081 MEDLINE
DOCUMENT NUMBER: 20144081 PubMed ID: 10677501
TITLE: A functional genetic screen identifies regions at the **C-terminal** tail and death-**domain** of death-associated protein **kinase** that are critical for its proapoptotic activity.
AUTHOR: Raveh T; Berissi H; Eisenstein M; Spivak T; Kimchi A
CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel.
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (2000 Feb 15) 97 (4) 1572-7.
Journal code: PV3; 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200003
ENTRY DATE: Entered STN: 20000330
Last Updated on STN: 20000330
Entered Medline: 20000323

AB Death-associated protein **kinase** (DAP-**kinase**) is a

Ca(+2)/**calmodulin**-regulated **serine/threonine kinase** with a multidomain structure that participates in **apoptosis** induced by a variety of signals. To identify regions in this protein that are critical for its proapoptotic activity, we performed a genetic screen on the basis of functional selection of short DAP-**kinase**-derived fragments that could protect cells from **apoptosis** by acting in a dominant-negative manner. We expressed a library of randomly fragmented DAP-**kinase** cDNA in HeLa cells and treated these cells with IFN-gamma to induce **apoptosis**. Functional cDNA fragments were recovered from cells that survived the selection, and those in the sense orientation were examined further in a secondary screen for their ability to protect cells from DAP-**kinase**-dependent tumor necrosis factor-alpha-induced **apoptosis**. We isolated four biologically active peptides that mapped to the ankyrin repeats, the "linker" region, the death **domain**, and the **C-terminal** tail of DAP-**kinase**. Molecular modeling of the complete death **domain** provided a structural basis for the function of the death-**domain** -derived fragment by suggesting that the protective fragment constitutes a distinct substructure. The last fragment, spanning the **C-terminal serine**-rich tail, defined a new regulatory region. Ectopic expression of the tail peptide (17 amino acids) inhibited the function of DAP-**kinase**, whereas removal of this region from the complete protein caused enhancement of the killing activity, indicating that the **C-terminal** tail normally plays a negative regulatory role. Altogether, this unbiased screen highlighted functionally important regions in the protein and revealed an additional level of regulation of DAP-**kinase** apoptotic function that does not affect the catalytic activity.

L16 ANSWER 8 OF 17 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 2000094983 MEDLINE
DOCUMENT NUMBER: 20094983 PubMed ID: 10629061
TITLE: Death-associated protein **kinase**-related protein 1, a novel **serine/threonine kinase** involved in **apoptosis**.
AUTHOR: Inbal B; Shani G; Cohen O; Kissil J L; Kimchi A
CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel.
SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (2000 Feb) 20 (3) 1044-54. Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 20000229
Last Updated on STN: 20020420
Entered Medline: 20000214

AB In this study we describe the identification and structure-function analysis of a novel death-associated protein (DAP) **kinase** -related protein, DRP-1. DRP-1 is a 42-kDa Ca(2+)/**calmodulin** (CaM)-regulated **serine threonine kinase** which shows high degree of homology to DAP **kinase**. The region of homology spans the catalytic **domain** and the CaM-regulatory region, whereas the remaining **C-terminal** part of the protein differs completely from DAP **kinase** and displays no homology to any known protein. The catalytic **domain** is also homologous to the recently identified ZIP **kinase** and to a lesser extent to the catalytic **domains** of DRAK1 and -2. Thus, DAP **kinase** DRP-1, ZIP **kinase**, and DRAK1/2 together form a novel subfamily of **serine/threonine kinases**.

DRP-1 is localized to the cytoplasm, as shown by immunostaining and cellular fractionation assays. It binds to CaM, undergoes autophosphorylation, and phosphorylates an exogenous substrate, the myosin light chain, in a Ca(2+)/CaM-dependent manner. The truncated protein, deleted of the CaM-regulatory **domain**, was converted into a constitutively active **kinase**. Ectopically expressed DRP-1 induced **apoptosis** in various types of cells. Cell killing by DRP-1 was dependent on two features: the status of the catalytic activity, and the presence of the **C-terminal** 40 amino acids shown to be required for self-dimerization of the **kinase**. Interestingly, further deletion of the CaM-regulatory region could override the indispensable role of the **C-terminal** tail in **apoptosis** and generated a "superkiller" mutant. A dominant negative fragment of DAP **kinase** encompassing the death **domain** was found to block **apoptosis** induced by DRP-1. Conversely, a catalytically inactive mutant of DRP-1, which functioned in a dominant negative manner, was significantly less effective in blocking **cell death** induced by DAP **kinase**. Possible functional connections between DAP **kinase** and DRP-1 are discussed.

L16 ANSWER 9 OF 17 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 2000481058 MEDLINE
DOCUMENT NUMBER: 20431384 PubMed ID: 10976872
TITLE: Activation of calcium/**calmodulin** regulated **kinases**.
AUTHOR: Wilmann M; Gautel M; Mayans O
CORPORATE SOURCE: EMBL, Hamburg, Germany.. wilmanns@embl-hamburg.de
SOURCE: CELLULAR AND MOLECULAR BIOLOGY, (2000 Jul) 46 (5) 883-94. Journal code: BNA; 9216789. ISSN: 0145-5680.
PUB. COUNTRY: France
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200010
ENTRY DATE: Entered STN: 20001019
Last Updated on STN: 20001019
Entered Medline: 20001012

AB Among numerous protein **kinases** found in mammalian cell systems there is a distinct subfamily of **serine/threonine kinases** that are regulated by **calmodulin** or other related activators in a calcium concentration dependent manner. Members of this family are involved in various cellular processes like cell proliferation and **death, cell** motility and metabolic pathways. In this contribution we shall review the available structural biology data on five members of this **kinase** family (calcium/**calmodulin** dependent **kinase**, twitchin **kinase**, titin **kinase**, phosphorylase **kinase**, myosin light chain **kinase**). As a common element, all these **kinases** contain a regulatory tail, which is **C-terminal** to their catalytic **domain**. The available 3D structures of two members, the **serine/threonine kinases** of the giant muscle proteins twitchin and titin in the autoinhibited conformation, show how this regulatory tail blocks their active sites. The structures suggest that activation of these **kinases** requires unblocking the active site from the **C-terminal** extension and conformational rearrangement of the active site loops. Small angle scattering data for myosin light chain **kinase** indicate a complete release of the **C-terminal** extension upon calcium/**calmodulin** binding. In addition, members of this family are regulated by diverse add-on mechanisms, including phosphorylation of residues within the activation segment or the P+1 loop as well as by additional regulatory

subunits. The available structural data lead to the hypothesis of two different activation mechanisms upon binding to calcium sensitive proteins. In one model, the regulatory tail is entirely released ("fall-apart"). The alternative model ("looping-out") proposes a two-anchored release mechanism.

L16 ANSWER 10 OF 17 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2000:430068 BIOSIS
DOCUMENT NUMBER: PREV200000430068
TITLE: Activation of calcium/**calmodulin** regulated **kinases**.
AUTHOR(S): Wilmanns, Mathias (1); Gautel, Mathias; Mayans, Olga
CORPORATE SOURCE: (1) EMBL c/o DESY, Notkestrasse 85, D-22603, Hamburg Germany
SOURCE: Cellular and Molecular Biology (Noisy-Le-Grand), (July, 2000) Vol. 46, No. 5, pp. 883-894. print.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Among numerous protein **kinases** found in mammalian cell systems there is a distinct subfamily of **serine/threonine kinases** that are regulated by **calmodulin** or other related activators in a calcium concentration dependent manner. Members of this family are involved in various cellular processes like cell proliferation and **death, cell** motility and metabolic pathways. In this contribution we shall review the available structural biology data on five members of this **kinase** family (calcium / **calmodulin** dependent **kinase,** twitchin **kinase,** titin **kinase,** phosphorylase **kinase,** myosin light chain **kinase**). As a common element, all these **kinases** contain a regulatory tail, which is **C-terminal** to their catalytic **domain**. The available 3D structures of two members, the **serine/threonine kinases** of the giant muscle protein twitchin and titin in the autoinhibited conformation, show how this regulatory tail blocks their active sites. The structures suggest that activation of these **kinases** requires unblocking the active site from the **C-terminal** extension and conformational rearrangement of the active site loops. Small angle scattering data for myosin light chain **kinase** indicate a complete release of the **C-terminal** extension upon calcium / **calmodulin** binding. In addition, members of this family are regulated by diverse add-on mechanisms, including phosphorylation of residues within the activation segment or the P+1 loop as well as by additional regulatory subunits. The available structural data lead to the hypothesis of two different activation mechanisms upon binding to calcium sensitive proteins. In one model, the regulatory tail is entirely released ("fall-apart"). The alternative model ("looping-out") proposes a two-anchored release mechanism.

L16 ANSWER 11 OF 17 MEDLINE
ACCESSION NUMBER: 1999430101 MEDLINE
DOCUMENT NUMBER: 99430101 PubMed ID: 10498871
TITLE: Requirement of protein **kinase** (Krs/MST) activation for MT-21-induced **apoptosis**.
AUTHOR: Watabe M; Kakeya H; Osada H
CORPORATE SOURCE: Laboratory of Antibiotics, The Institute of Physical and Chemical Research (RIKEN), 2-1 Hirosawa, Wako, Saitama 351-0198, Japan.
SOURCE: ONCOGENE, (1999 Sep 16) 18 (37) 5211-20. Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199910
ENTRY DATE: Entered STN: 19991101
Last Updated on STN: 20020420
Entered Medline: 19991021

AB Fas is a well characterized **apoptosis**-inducing factor. One of our synthetic compounds, MT-21, induced **apoptosis** in human leukemia HL-60 cells similar to Fas. MT-21 activated caspase-3, an important cysteine aspartic protease for **apoptosis** induction. MT-21 also activated c-Jun-NH2-terminal **kinase** (JNK), a member of mitogen activated protein **kinase** (MAPK) superfamily that is involved in the regulation of cell growth, differentiation and **cell death**. Moreover, MT-21 treatment resulted in the activation of a 36 kDa **kinase** which uses myelin basic protein (MBP) as a substrate. However, MAPK and p38 were not activated by treatment with MT-21. The 36 kDa MBP **kinase** was shown to be a proteolytic product derived from the Krs protein with a molecular weight of 60 kDa. The Krs protein is a Ser/Thr protein **kinase** whose activity is enhanced by digestion of its **C-terminal** regulatory **domain** by caspase-3. When a **kinase**-inactive mutant form of Krs protein was overexpressed in HL-60 cells, JNK activation and **apoptosis** induction by MT-21 were suppressed. Furthermore, overexpression of dominant negative c-Jun also suppressed **apoptosis** induction by MT-21. These findings indicate that MT-21 induces **apoptosis** by the activation of JNK via the Krs protein, which is activated by caspase cleavage.

L16 ANSWER 12 OF 17 MEDLINE
ACCESSION NUMBER: 1999164089 MEDLINE
DOCUMENT NUMBER: 99164089 PubMed ID: 10064589
TITLE: **Apoptosis** inhibitory activity of cytoplasmic p21(Cip1/WAF1) in monocytic differentiation.
AUTHOR: Asada M; Yamada T; Ichijo H; Delia D; Miyazono K; Fukumuro K; Mizutani S
CORPORATE SOURCE: Department of Virology, The National Children's Medical Research Center, 3-35-31, Taishido, Setagaya-ku, Tokyo, 154, Japan.
SOURCE: EMBO JOURNAL, (1999 Mar 1) 18 (5) 1223-34.
Journal code: EMB; 8208664. ISSN: 0261-4189.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199904
ENTRY DATE: Entered STN: 19990511
Last Updated on STN: 20000303
Entered Medline: 19990429

AB p21(Cip1/WAF1) inhibits cell-cycle progression by binding to G1 cyclin/CDK complexes and proliferating cell nuclear antigen (PCNA) through its N- and **C-terminal domains**, respectively. The cell-cycle inhibitory activity of p21(Cip1/WAF1) is correlated with its nuclear localization. Here, we report a novel cytoplasmic localization of p21(Cip1/WAF1) in peripheral blood monocytes (PBMs) and in U937 cells undergoing monocytic differentiation by in vitro treatment with vitamin D3 or ectopic expression of p21(Cip1/WAF1), and analyze the biological consequences of this cytoplasmic expression. U937 cells which exhibit nuclear p21(Cip1/WAF1) demonstrated G1 cell-cycle arrest and subsequently differentiated into monocytes. The latter event was associated with a cytoplasmic expression of nuclear p21(Cip1/WAF1), concomitantly with a resistance to various apoptogenic stimuli. Biochemical analysis showed that cytoplasmic p21(Cip1/WAF1) forms a complex with the **apoptosis**

signal-regulating **kinase** 1 (ASK1) and inhibits stress-activated MAP **kinase** cascade. Expression of a deletion mutant of p21(Cip1/WAF1) lacking the nuclear localization signal (DeltaNLS-p21) did not induce cell cycle arrest nor monocytic differentiation, but led to an **apoptosis**-resistant phenotype, mediated by binding to and inhibition of the stress-activated ASK1 activity. Thus, cytoplasmic p21(Cip1/WAF1) itself acted as an inhibitor of **apoptosis**. Our findings highlight the different functional roles of p21(Cip1/WAF1), which are determined by its intracellular distribution and are dependent on the stage of differentiation.

L16 ANSWER 13 OF 17 MEDLINE
ACCESSION NUMBER: 2000029738 MEDLINE
DOCUMENT NUMBER: 20029738 PubMed ID: 10561491
TITLE: Hematopoietic lineage cell specific protein 1 associates with and down-regulates protein **kinase** CK2.
AUTHOR: Ruzzene M; Brunati A M; Sarno S; Donella-Deana A; Pinna L A
CORPORATE SOURCE: Dipartimento di Chimica Biologica and Centro per lo Studio delle Biomembrane del CNR, University of Padova, Viale G. Colombo, 335121, Padova, Italy.
SOURCE: FEBS LETTERS, (1999 Nov 12) 461 (1-2) 32-6.
Journal code: 0155157. ISSN: 0014-5793.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199912
ENTRY DATE: Entered STN: 20000113
Last Updated on STN: 20020420
Entered Medline: 19991214

AB The catalytic (alpha) subunit of protein **kinase** CK2 and the hematopoietic specific protein 1 (HS1) display opposite effects on Ha-ras induced fibroblast transformation, by enhancing and counteracting it, respectively. Here we show the occurrence of physical association between HS1 and CK2alpha as judged from both far Western blot and plasmon resonance (BIAcore) analysis. Association of HS1 with CK2alpha is drastically reduced by the deletion of the HS1 **C-terminal** region (403-486) containing an SH3 **domain**. HS1, but not its deletion mutant HS1 Delta324-393, lacking a sequence similar to an acidic stretch of the regulatory beta-subunit of CK2, inhibits **calmodulin** phosphorylation by CK2alpha. These data indicate that HS1 physically interacts with CK2alpha and down-regulates its activity by a mechanism similar to the beta-subunit.

L16 ANSWER 14 OF 17 MEDLINE
ACCESSION NUMBER: 1999003259 MEDLINE
DOCUMENT NUMBER: 99003259 PubMed ID: 9786912
TITLE: DRAKs, novel **serine/threonine kinases** related to death-associated protein **kinase** that trigger **apoptosis**.
AUTHOR: Sanjo H; Kawai T; Akira S
CORPORATE SOURCE: Department of Biochemistry, Hyogo College of Medicine, 1-1 Mukogawa-cho, Nishinomiya, Hyogo 663-8501, Japan.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1998 Oct 30) 273 (44) 29066-71.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AB011420; GENBANK-AB011421
ENTRY MONTH: 199812

ENTRY DATE: Entered STN: 19990115
Last Updated on STN: 20020420
Entered Medline: 19981201

AB The present study describes the cloning of two novel **serine/threonine kinases** termed DRAK1 and DRAK2, whose catalytic **domains** are related to that of death-associated protein **kinase**, a **serine/threonine kinase** involved in **apoptosis**. Both DRAKs are composed of the N-terminal catalytic **domain** and the **C-terminal domain** that is responsible for regulation of **kinase** activity. DRAK1 and DRAK2 show 59.7% identity and display ubiquitous expression. An in vitro **kinase** assay revealed that both DRAKs are autophosphorylated and phosphorylate myosin light chain as an exogenous substrate, although the **kinase** activity of DRAK2 is significantly lower than that of DRAK1. Both DRAKs are exclusively localized to the nucleus. Furthermore, overexpression of both DRAKs induces the morphological changes of **apoptosis** in NIH 3T3 cells, suggesting the role of DRAKs in apoptotic signaling.

L16 ANSWER 15 OF 17 MEDLINE
ACCESSION NUMBER: 1998211933 MEDLINE
DOCUMENT NUMBER: 98211933 PubMed ID: 9545236
TITLE: Caspase-mediated activation and induction of **apoptosis** by the mammalian Ste20-like **kinase** Mst1.
AUTHOR: Graves J D; Gotoh Y; Draves K E; Ambrose D; Han D K; Wright M; Chernoff J; Clark E A; Krebs E G
CORPORATE SOURCE: Department of Immunology, University of Washington Medical Center, Seattle, WA 98109, USA.
CONTRACT NUMBER: GM37905 (NIGMS)
GM42508 (NIGMS)
SOURCE: EMBO JOURNAL, (1998 Apr 15) 17 (8) 2224-34.
Journal code: 8208664. ISSN: 0261-4189.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199806
ENTRY DATE: Entered STN: 19980708
Last Updated on STN: 20020420
Entered Medline: 19980624

AB Mst1 is a ubiquitously expressed **serine-threonine kinase**, homologous to the budding yeast Ste20, whose physiological regulation and cellular function are unknown. In this paper we show that Mst1 is specifically cleaved by a caspase 3-like activity during **apoptosis** induced by either cross-linking CD95/Fas or by staurosporine treatment. CD95/Fas-induced cleavage of Mst1 was blocked by the cysteine protease inhibitor ZVAD-fmk, the more selective caspase inhibitor DEVD-CHO and by the viral serpin CrmA. Caspase-mediated cleavage of Mst1 removes the **C-terminal** regulatory **domain** and correlates with an increase in Mst1 activity in vivo, consistent with caspase-mediated cleavage activating Mst1. Overexpression of either wild-type Mst1 or a truncated mutant induces morphological changes characteristic of **apoptosis**. Furthermore, exogenously expressed Mst1 is cleaved, indicating that Mst1 can activate caspases that result in its cleavage. **Kinase**-dead Mst1 did not induce morphological alterations and was not cleaved upon overexpression, indicating that Mst1 must be catalytically active in order to mediate these effects. Mst1 activates MKK6, p38 MAPK, MKK7 and SAPK in co-transfection assays, suggesting that Mst1 may activate these pathways. Our findings suggest the existence of a positive feedback loop involving Mst1, and possibly the SAPK and p38 MAPK pathways, which serves to amplify

the apoptotic response.

L16 ANSWER 16 OF 17 MEDLINE
ACCESSION NUMBER: 1998416694 MEDLINE
DOCUMENT NUMBER: 98416694 PubMed ID: 9739089
TITLE: Crystal structure of JNK3: a **kinase** implicated in neuronal **apoptosis**.
AUTHOR: Xie X; Gu Y; Fox T; Coll J T; Fleming M A; Markland W; Caron P R; Wilson K P; Su M S
CORPORATE SOURCE: Vertex Pharmaceuticals Incorporated, Cambridge, MA 02139-4211, USA.
SOURCE: STRUCTURE, (1998 Aug 15) 6 (8) 983-91.
Journal code: B31; 9418985. ISSN: 0969-2126.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: PDB-1JNK
ENTRY MONTH: 199812
ENTRY DATE: Entered STN: 19990115
Last Updated on STN: 20000303
Entered Medline: 19981208

AB BACKGROUND: The c-Jun N-terminal **kinases** (JNKs) are members of the mitogen-activated protein (MAP) **kinase** family, and regulate signal transduction in response to environmental stress. Activation and nuclear localization of JNK3, a neuronal-specific isoform of JNK, has been associated with hypoxic and ischemic damage of CA1 neurons in the hippocampus. Knockout mice lacking JNK3 showed reduced **apoptosis** of hippocampal neurons and reduced seizure induced by kainic acid, a glutamate-receptor agonist. Thus, JNK3 may be important in the pathology of neurological disorders and is of significant medical interest. RESULTS: We report here the structure of unphosphorylated JNK3 in complex with adenylyl imidodiphosphate, an ATP analog. JNK3 has a typical **kinase** fold, with the ATP-binding site situated within a cleft between the N- and **C-terminal domains**. In contrast to other known MAP **kinase** structures, the ATP-binding site of JNK3 is well ordered; the glycine-rich nucleotide-binding sequence forms a beta-strand-turn-beta-strand structure over the nucleotide. Unphosphorylated JNK3 assumes an open conformation, in which the N- and **C-terminal domains** are twisted apart relative to their positions in cAMP-dependent protein **kinase**. The rotation leads to the misalignment of some of the catalytic residues. The phosphorylation lip of JNK3 partially blocks the substrate-binding site. CONCLUSIONS: This is the first JNK structure to be determined, providing a unique opportunity to compare structures from the three MAP **kinase** subfamilies. The structure reveals atomic-level details of the shape of JNK3 and the interactions between the **kinase** and the nucleotide. The misalignment of catalytic residues and occlusion of the active site by the phosphorylation lip may account for the low activity of unphosphorylated JNK3. The structure provides a framework for understanding the substrate specificity of different JNK isoforms, and should aid the design of selective JNK3 inhibitors.

L16 ANSWER 17 OF 17 MEDLINE
ACCESSION NUMBER: 97474480 MEDLINE
DOCUMENT NUMBER: 97474480 PubMed ID: 9335504
TITLE: Opposing BMP and EGF signalling pathways converge on the TGF-beta family mediator Smad1.
AUTHOR: Kretzschmar M; Doody J; Massague J
CORPORATE SOURCE: Cell Biology and Genetics Program, Memorial Sloan-Kettering Cancer Center, New York, New York 10021, USA.
SOURCE: NATURE, (1997 Oct 9) 389 (6651) 618-22.

Journal code: NSC; 0410462. ISSN: 0028-0836.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199711
ENTRY DATE: Entered STN: 19971224
Last Updated on STN: 20000303
Entered Medline: 19971103

AB The growth factor TGF-beta, bone morphogenetic proteins (BMPs) and related factors regulate cell proliferation, differentiation and **apoptosis**, controlling the development and maintenance of most tissues. Their signals are transmitted through the phosphorylation of the tumour-suppressor SMAD proteins by receptor protein **serine/threonine kinases** (RS/TKs), leading to the nuclear accumulation and transcriptional activity of SMAD proteins. Here we report that Smad1, which mediates BMP signals, is also a target of mitogenic growth-factor signalling through epidermal growth factor and hepatocyte growth factor receptor protein tyrosine **kinases** (RTKs). Phosphorylation occurs at specific **serines** within the region linking the inhibitory and effector **domains** of Smad1, and is catalysed by the Erk family of mitogen-activated protein **kinases**. In contrast to the BMP-stimulated phosphorylation of Smad1, which affects **carboxy-terminal serines** and induces nuclear accumulation of Smad1, Erk-mediated phosphorylation specifically inhibits the nuclear accumulation of Smad1. Thus, Smad1 receives opposing regulatory inputs through RTKs and RS/TKs, and it is this balance that determines the level of Smad1 activity in the nucleus, and so possibly the role of Smad1 in the control of cell fate.

```
=> s "DAP"
L17      10019 "DAP"

=> d his

     (FILE 'HOME' ENTERED AT 13:40:52 ON 05 JUN 2002)

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 13:41:17 ON 05 JUN 2002
L1             0 S CALMODULAIN
L2        110146 S CALMODULIN
L3        342878 S SERINE OR THREONINE
L4         73725 S L3 AND KINASE
L5          6021 S L2 AND L4
L6        422053 S (CELL (A) DEATH) OR APOPTOSIS
L7           391 S L5 AND L6
L8           195 S HUMAN AND L7
L9       1023024 S DOMAIN?
L10          111 S L7 AND L9
L11          345 S DAP(A)KINASE?
L12           72 S L10 AND L11
L13           23 DUP REM L12 (49 DUPLICATES REMOVED)
L14       255022 S CARBOXY(W) TERMINAL OR CARBOXY (W)END OR C-TERMINAL
L15           34 S L10 AND L14
L16           17 DUP REM L15 (17 DUPLICATES REMOVED)
L17        10019 S "DAP"

=> s l16 and l17
L18            6 L16 AND L17

=> d 1-6 ibib ab
```

L18 ANSWER 1 OF 6 MEDLINE
ACCESSION NUMBER: 2001434353 MEDLINE
DOCUMENT NUMBER: 21214809 PubMed ID: 11313698
TITLE: **DAP-kinase**: from functional gene cloning to establishment of its role in **apoptosis** and cancer.
AUTHOR: Cohen O; Kimchi A
CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel.
SOURCE: CELL DEATH AND DIFFERENTIATION, (2001 Jan) 8 (1) 6-15. Ref: 39
Journal code: C7U; 9437445. ISSN: 1350-9047.
PUB. COUNTRY: England: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010806
Last Updated on STN: 20010806
Entered Medline: 20010802

AB **DAP-kinase** is a pro-apoptotic Ca(2+) **calmodulin**-regulated **serine/threonine kinase** that participates in a wide array of apoptotic systems initiated by interferon-gamma, TNF-alpha, activated Fas, and detachment from extracellular matrix. It was isolated by an unbiased functional approach to gene cloning aimed at hitting central mediators of the apoptotic process. This 160 Kd protein **kinase** is localized to actin microfilaments and carries interesting modules such as ankyrin repeats and the death **domain**. The death promoting effects of **DAP-kinase** depend on its intact catalytic activity, the correct intracellular localization, and on the presence of the death **domain**. A few mechanisms restrain the killing effects of the protein in healthy cells. The enzyme's active site is negatively controlled by an adjacent CaM regulatory **domain** whose effect is relieved by binding to Ca(2+)-activated **calmodulin**. A second mode of autoinhibition engages the **serine**-rich **C-terminal** tail, spanning the last 17 amino acids of the protein. A link between **DAP-kinase** and cancer has been established. It was found that the mRNA and protein expression is frequently lost in various human cancer cell lines. Analysis of the methylation status of **DAP-kinase**'s 5' UTR in DNA extracted from fresh tumor samples, showed high incidence of hypermethylation in several human carcinomas and B cell malignancies. The anti-tumorigenic effect of **DAP-kinase** was also studied experimentally in mouse model systems where the re-introduction of **DAP-kinase** into highly metastatic mouse lung carcinoma cells who had lost the protein, strongly reduced their metastatic capacity. Thus, it appears that loss of **DAP-kinase** confers a selective advantage to cancer cells and may play a causative role in tumor progression. A few novel **kinases** sharing high homology in their catalytic **domains** with **DAP-kinase** have been recently identified constituting altogether a novel family of death promoting **serine/threonine kinases**.

L18 ANSWER 2 OF 6 MEDLINE
ACCESSION NUMBER: 2001169641 MEDLINE
DOCUMENT NUMBER: 21167344 PubMed ID: 11268041
TITLE: The **DAP kinase** family of pro-apoptotic

proteins: novel players in the apoptotic game.
AUTHOR: Kogel D; Prehn J H; Scheidtmann K H
CORPORATE SOURCE: Interdisciplinary Center for Clinical Research (IZKF), University of Munster, Germany.. koegel@uni-muenster.de
SOURCE: BIOESSAYS, (2001 Apr) 23 (4) 352-8. Ref: 47
Journal code: 9YY; 8510851. ISSN: 0265-9247.
PUB. COUNTRY: England: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200105
ENTRY DATE: Entered STN: 20010604
Last Updated on STN: 20010604
Entered Medline: 20010531

AB The **DAP** (Death Associated Protein) **kinase** family is a novel subfamily of pro-apoptotic **serine/threonine kinases**. All five **DAP kinase** family members identified to date are ubiquitously expressed in various tissues and are capable of inducing **apoptosis**. The sequence homology of the five **kinases** is largely restricted to the N-terminal **kinase domain**. In contrast, the adjacent **C-terminal** regions are very diverse and link individual family members to specific signal transduction pathways. There is increasing evidence that **DAP kinase** family members are involved in both extrinsic and intrinsic pathways of **apoptosis** and may play a role in tumor progression. This review will focus on structural composition and subcellular localization of **DAP kinase** family members and on signal transduction pathways leading to their activation. Potential mechanisms of **DAP kinase** family-mediated **apoptosis** will be discussed. BioEssays 23:352-358, 2001. Copyright 2001 John Wiley & Sons, Inc.

L18 ANSWER 3 OF 6 MEDLINE
ACCESSION NUMBER: 2000144081 MEDLINE
DOCUMENT NUMBER: 20144081 PubMed ID: 10677501
TITLE: A functional genetic screen identifies regions at the **C-terminal** tail and death-**domain** of death-associated protein **kinase** that are critical for its proapoptotic activity.
AUTHOR: Raveh T; Berissi H; Eisenstein M; Spivak T; Kimchi A
CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel.
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (2000 Feb 15) 97 (4) 1572-7.
Journal code: PV3; 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200003
ENTRY DATE: Entered STN: 20000330
Last Updated on STN: 20000330
Entered Medline: 20000323

AB Death-associated protein **kinase** (**DAP-kinase**) is a Ca(+2)/**calmodulin**-regulated **serine/threonine kinase** with a multidomain structure that participates in **apoptosis** induced by a variety of signals. To identify regions in this protein that are critical for its proapoptotic activity, we performed a genetic screen on the basis of functional selection of short **DAP-kinase**-derived fragments that

could protect cells from **apoptosis** by acting in a dominant-negative manner. We expressed a library of randomly fragmented **DAP-kinase** cDNA in HeLa cells and treated these cells with IFN-gamma to induce **apoptosis**. Functional cDNA fragments were recovered from cells that survived the selection, and those in the sense orientation were examined further in a secondary screen for their ability to protect cells from **DAP-kinase**-dependent tumor necrosis factor-alpha-induced **apoptosis**. We isolated four biologically active peptides that mapped to the ankyrin repeats, the "linker" region, the death **domain**, and the **C-terminal** tail of **DAP-kinase**. Molecular modeling of the complete death **domain** provided a structural basis for the function of the death-**domain**-derived fragment by suggesting that the protective fragment constitutes a distinct substructure. The last fragment, spanning the **C-terminal serine**-rich tail, defined a new regulatory region. Ectopic expression of the tail peptide (17 amino acids) inhibited the function of **DAP-kinase**, whereas removal of this region from the complete protein caused enhancement of the killing activity, indicating that the **C-terminal** tail normally plays a negative regulatory role. Altogether, this unbiased screen highlighted functionally important regions in the protein and revealed an additional level of regulation of **DAP-kinase** apoptotic function that does not affect the catalytic activity.

L18 ANSWER 4 OF 6 MEDLINE
ACCESSION NUMBER: 2000094983 MEDLINE
DOCUMENT NUMBER: 20094983 PubMed ID: 10629061
TITLE: Death-associated protein **kinase**-related protein 1, a novel **serine/threonine kinase** involved in **apoptosis**.
AUTHOR: Inbal B; Shani G; Cohen O; Kissil J L; Kimchi A
CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel.
SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (2000 Feb) 20 (3) 1044-54. Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 20000229
Last Updated on STN: 20020420
Entered Medline: 20000214

AB In this study we describe the identification and structure-function analysis of a novel death-associated protein (**DAP**) **kinase**-related protein, DRP-1. DRP-1 is a 42-kDa Ca(2+)/**calmodulin** (CaM)-regulated **serine threonine kinase** which shows high degree of homology to **DAP kinase**. The region of homology spans the catalytic **domain** and the CaM-regulatory region, whereas the remaining **C-terminal** part of the protein differs completely from **DAP kinase** and displays no homology to any known protein. The catalytic **domain** is also homologous to the recently identified ZIP **kinase** and to a lesser extent to the catalytic **domains** of DRAK1 and -2. Thus, **DAP kinase** DRP-1, ZIP **kinase**, and DRAK1/2 together form a novel subfamily of **serine/threonine kinases**. DRP-1 is localized to the cytoplasm, as shown by immunostaining and cellular fractionation assays. It binds to CaM, undergoes autophosphorylation, and phosphorylates an exogenous substrate, the myosin light chain, in a Ca(2+)/CaM-dependent manner. The truncated protein, deleted of the

CaM-regulatory **domain**, was converted into a constitutively active **kinase**. Ectopically expressed DRP-1 induced **apoptosis** in various types of cells. Cell killing by DRP-1 was dependent on two features: the status of the catalytic activity, and the presence of the **C-terminal** 40 amino acids shown to be required for self-dimerization of the **kinase**. Interestingly, further deletion of the CaM-regulatory region could override the indispensable role of the **C-terminal** tail in **apoptosis** and generated a "superkiller" mutant. A dominant negative fragment of **DAP kinase** encompassing the death **domain** was found to block **apoptosis** induced by DRP-1. Conversely, a catalytically inactive mutant of DRP-1, which functioned in a dominant negative manner, was significantly less effective in blocking **cell death** induced by **DAP kinase**. Possible functional connections between **DAP kinase** and DRP-1 are discussed.

L18 ANSWER 5 OF 6 MEDLINE
ACCESSION NUMBER: 1999003259 MEDLINE
DOCUMENT NUMBER: 99003259 PubMed ID: 9786912
TITLE: DRAKs, novel **serine/threonine kinases** related to death-associated protein **kinase** that trigger **apoptosis**.
AUTHOR: Sanjo H; Kawai T; Akira S
CORPORATE SOURCE: Department of Biochemistry, Hyogo College of Medicine, 1-1 Mukogawa-cho, Nishinomiya, Hyogo 663-8501, Japan.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1998 Oct 30) 273 (44) 29066-71.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AB011420; GENBANK-AB011421
ENTRY MONTH: 199812
ENTRY DATE: Entered STN: 19990115
Last Updated on STN: 20020420
Entered Medline: 19981201

AB The present study describes the cloning of two novel **serine/threonine kinases** termed DRAK1 and DRAK2, whose catalytic **domains** are related to that of death-associated protein **kinase**, a **serine/threonine kinase** involved in **apoptosis**. Both DRAKs are composed of the N-terminal catalytic **domain** and the **C-terminal domain** that is responsible for regulation of **kinase** activity. DRAK1 and DRAK2 show 59.7% identity and display ubiquitous expression. An in vitro **kinase** assay revealed that both DRAKs are autophosphorylated and phosphorylate myosin light chain as an exogenous substrate, although the **kinase** activity of DRAK2 is significantly lower than that of DRAK1. Both DRAKs are exclusively localized to the nucleus. Furthermore, overexpression of both DRAKs induces the morphological changes of **apoptosis** in NIH 3T3 cells, suggesting the role of DRAKs in apoptotic signaling.

L18 ANSWER 6 OF 6 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 2002:89428 SCISEARCH
THE GENUINE ARTICLE: 513UP
TITLE: **DAP kinase** activity is critical for C-2-ceramide-induced **apoptosis** in PC12 cells
AUTHOR: Yamamoto M (Reprint); Hioki T; Ishii T; Nakajima-Iijima S; Uchino S
CORPORATE SOURCE: Mitsubishi Tokyo Pharmaceut Inc, Yokohama Res Ctr,

Pharmaceut Discovery Lab, Aoba Ku, 1000 Kamoshida, Yokohama, Kanagawa 2278502, Japan (Reprint); Mitsubishi Tokyo Pharmaceut Inc, Yokohama Res Ctr, Pharmaceut Discovery Lab, Aoba Ku, Yokohama, Kanagawa 2278502, Japan

COUNTRY OF AUTHOR: Japan
SOURCE: EUROPEAN JOURNAL OF BIOCHEMISTRY, (JAN 2002) Vol. 269, No. 1, pp. 139-147.
Publisher: BLACKWELL SCIENCE LTD, P O BOX 88, OSNEY MEAD, OXFORD OX2 0NE, OXON, ENGLAND.
ISSN: 0014-2956.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 41

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Exposure of PC12 cells to C-2-ceramide results in dose-dependent **apoptosis**. Here, we investigate the involvement of death-associated protein (**DAP**) **kinase**, initially identified as a positive mediator of the interferon-gamma-induced **apoptosis** of HeLa cells, in the C-2-ceramide-induced **apoptosis** of PC 12 cells. **DAP kinase** is endogenously expressed in these cells. On exposure of PC 12 cells to 30 muM C-2-ceramide, both the total (assayed in the presence of Ca2+/**calmodulin**) and Ca2+/**calmodulin**-independent (assayed in the presence of EGTA) **DAP kinase** activities were transiently increased 5.0- and 12.2-fold, respectively, at 10 min, and then decreased to 1.7- and 3.4-fold at 90 min. After 10 min exposure to 30 mum C-2-ceramide, the Ca2+/**calmodulin** independent activity/total activity ratio increased from 0.22 to 0.60. These effects were dependent on the C-2-ceramide concentration. C-8-ceramide, another active ceramide analog, also induced **apoptosis** and activated **DAP kinase**, while C-2-dihydroceramide, an inactive ceramide analog, failed to induce **apoptosis** and increase **DAP kinase** activity. Furthermore, transfection studies revealed that overexpression of wild-type **DAP kinase** enhanced the sensitivity to C-2- and C-8-ceramide, while a catalytically inactive **DAP kinase** mutant and a construct containing the death **domain** and **C-terminal** tail of **DAP kinase**, which act in a dominant-negative manner, rescued cells from C-2-, and C-8-ceramide-induced **apoptosis**. These findings demonstrate that **DAP kinase** is an important component of the apoptotic machinery involved in ceramide-induced **apoptosis**, and that the intrinsic **DAP kinase** activity is critical for ceramide-induced **apoptosis**.

=> d his

(FILE 'HOME' ENTERED AT 13:40:52 ON 05 JUN 2002)

FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS, LIFESCI' ENTERED AT 13:41:17 ON 05 JUN 2002

L1	0	S	CALMODULAIN
L2	110146	S	CALMODULIN
L3	342878	S	SERINE OR THREONINE
L4	73725	S	L3 AND KINASE
L5	6021	S	L2 AND L4
L6	422053	S	(CELL (A) DEATH) OR APOPTOSIS
L7	391	S	L5 AND L6
L8	195	S	HUMAN AND L7
L9	1023024	S	DOMAIN?
L10	111	S	L7 AND L9
L11	345	S	DAP(A)KINASE?

L12 72 S L10 AND L11
L13 23 DUP REM L12 (49 DUPLICATES REMOVED)
L14 255022 S CARBOXY(W) TERMINAL OR CARBOXY (W)END OR C-TERMINAL
L15 34 S L10 AND L14
L16 17 DUP REM L15 (17 DUPLICATES REMOVED)
L17 10019 S "DAP"
L18 6 S L16 AND L17

=> s "zip"
L19 4269 "ZIP"

=> l16 and l19
L16 IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> s l16 and l19
L20 2 L16 AND L19

=> d 1-2 ibib ab

L20 ANSWER 1 OF 2 MEDLINE
ACCESSION NUMBER: 2000094983 MEDLINE
DOCUMENT NUMBER: 20094983 PubMed ID: 10629061
TITLE: Death-associated protein **kinase**-related protein 1, a novel **serine/threonine kinase** involved in **apoptosis**.
AUTHOR: Inbal B; Shani G; Cohen O; Kissil J L; Kimchi A
CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel.
SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (2000 Feb) 20 (3) 1044-54. Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 20000229
Last Updated on STN: 20020420
Entered Medline: 20000214

AB In this study we describe the identification and structure-function analysis of a novel death-associated protein (DAP) **kinase**-related protein, DRP-1. DRP-1 is a 42-kDa Ca(2+)/**calmodulin** (CaM)-regulated **serine threonine kinase** which shows high degree of homology to DAP **kinase**. The region of homology spans the catalytic **domain** and the CaM-regulatory region, whereas the remaining **C-terminal** part of the protein differs completely from DAP **kinase** and displays no homology to any known protein. The catalytic **domain** is also homologous to the recently identified **ZIP kinase** and to a lesser extent to the catalytic **domains** of DRAK1 and -2. Thus, DAP **kinase** DRP-1, **ZIP kinase**, and DRAK1/2 together form a novel subfamily of **serine/threonine kinases**. DRP-1 is localized to the cytoplasm, as shown by immunostaining and cellular fractionation assays. It binds to CaM, undergoes autophosphorylation, and phosphorylates an exogenous substrate, the myosin light chain, in a Ca(2+)/CaM-dependent manner. The truncated protein, deleted of the CaM-regulatory **domain**, was converted into a constitutively active **kinase**. Ectopically expressed DRP-1 induced **apoptosis** in various types of cells. Cell killing by DRP-1 was dependent on two features: the status of the

catalytic activity, and the presence of the **C-terminal** 40 amino acids shown to be required for self-dimerization of the **kinase**. Interestingly, further deletion of the CaM-regulatory region could override the indispensable role of the **C-terminal** tail in **apoptosis** and generated a "superkiller" mutant. A dominant negative fragment of DAP **kinase** encompassing the death **domain** was found to block **apoptosis** induced by DRP-1. Conversely, a catalytically inactive mutant of DRP-1, which functioned in a dominant negative manner, was significantly less effective in blocking **cell death** induced by DAP **kinase** . Possible functional connections between DAP **kinase** and DRP-1 are discussed.

L20 ANSWER 2 OF 2 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 2002:89428 SCISEARCH
THE GENUINE ARTICLE: 513UP
TITLE: DAP **kinase** activity is critical for C-2-ceramide-induced **apoptosis** in PC12 cells
AUTHOR: Yamamoto M (Reprint); Hioki T; Ishii T; Nakajima-Iijima S; Uchino S
CORPORATE SOURCE: Mitsubishi Tokyo Pharmaceut Inc, Yokohama Res Ctr, Pharmaceut Discovery Lab, Aoba Ku, 1000 Kamoshida, Yokohama, Kanagawa 2278502, Japan (Reprint); Mitsubishi Tokyo Pharmaceut Inc, Yokohama Res Ctr, Pharmaceut Discovery Lab, Aoba Ku, Yokohama, Kanagawa 2278502, Japan
COUNTRY OF AUTHOR: Japan
SOURCE: EUROPEAN JOURNAL OF BIOCHEMISTRY, (JAN 2002) Vol. 269, No. 1, pp. 139-147.
Publisher: BLACKWELL SCIENCE LTD, P O BOX 88, OSNEY MEAD, OXFORD OX2 0NE, OXON, ENGLAND.
ISSN: 0014-2956.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 41

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Exposure of PC12 cells to C-2-ceramide results in dose-dependent **apoptosis**. Here, we investigate the involvement of death-associated protein (DAP) **kinase**, initially identified as a positive mediator of the interferon-gamma-induced **apoptosis** of HeLa cells, in the C-2-ceramide-induced **apoptosis** of PC 12 cells. DAP **kinase** is endogenously expressed in these cells. On exposure of PC 12 cells to 30 muM C-2-ceramide, both the total (assayed in the presence of Ca2+/**calmodulin**) and Ca2+/**calmodulin** -independent (assayed in the presence of EGTA) DAP **kinase** activities were transiently increased 5.0- and 12.2-fold, respectively, at 10 min, and then decreased to 1.7- and 3.4-fold at 90 min. After 10 min exposure to 30 mum C-2-ceramide, the Ca2+/**calmodulin** independent activity/total activity ratio increased from 0.22 to 0.60. These effects were dependent on the C-2-ceramide concentration. C-8-ceramide, another active ceramide analog, also induced **apoptosis** and activated DAP **kinase**, while C-2-dihydroceramide, an inactive ceramide analog, failed to induce **apoptosis** and increase DAP **kinase** activity. Furthermore, transfection studies revealed that overexpression of wild-type DAP **kinase** enhanced the sensitivity to C-2- and C-8-ceramide, while a catalytically inactive DAP **kinase** mutant and a construct containing the death **domain** and **C-terminal** tail of DAP **kinase**, which act in a dominant-negative manner, rescued cells from C-2-, and C-8-ceramide-induced **apoptosis**. These findings demonstrate that DAP **kinase** is an important component of the apoptotic machinery involved in ceramide-induced **apoptosis**, and that the intrinsic DAP **kinase** activity is critical for ceramide-induced

apoptosis.

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=> s "DRP-1"
L21         98 "DRP-1"

=> d his

     (FILE 'HOME' ENTERED AT 13:40:52 ON 05 JUN 2002)

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 13:41:17 ON 05 JUN 2002
L1            0 S CALMODULAIN
L2       110146 S CALMODULIN
L3       342878 S SERINE OR THREONINE
L4        73725 S L3 AND KINASE
L5         6021 S L2 AND L4
L6       422053 S (CELL (A) DEATH) OR APOPTOSIS
L7          391 S L5 AND L6
L8          195 S HUMAN AND L7
L9      1023024 S DOMAIN?
L10         111 S L7 AND L9
L11         345 S DAP(A)KINASE?
L12          72 S L10 AND L11
L13          23 DUP REM L12 (49 DUPLICATES REMOVED)
L14      255022 S CARBOXY(W) TERMINAL OR CARBOXY (W)END OR C-TERMINAL
L15          34 S L10 AND L14
L16          17 DUP REM L15 (17 DUPLICATES REMOVED)
L17       10019 S "DAP"
L18           6 S L16 AND L17
L19        4269 S "ZIP"
L20           2 S L16 AND L19
L21          98 S "DRP-1"

=> s l16 and l21
L22           1 L16 AND L21

=> d all

L22  ANSWER 1 OF 1     MEDLINE
AN   2000094983     MEDLINE
DN   20094983   PubMed ID: 10629061
TI   Death-associated protein kinase-related protein 1, a novel
     serine/threonine kinase involved in
     apoptosis.
AU   Inbal B; Shani G; Cohen O; Kissil J L; Kimchi A
CS   Department of Molecular Genetics, Weizmann Institute of Science, Rehovot
     76100, Israel.
SO   MOLECULAR AND CELLULAR BIOLOGY, (2000 Feb) 20 (3) 1044-54.
     Journal code: 8109087. ISSN: 0270-7306.
CY   United States
DT   Journal; Article; (JOURNAL ARTICLE)
LA   English
FS   Priority Journals
EM   200002
ED   Entered STN: 20000229
     Last Updated on STN: 20020420
     Entered Medline: 20000214
AB   In this study we describe the identification and structure-function
     analysis of a novel death-associated protein (DAP) kinase
     -related protein, DRP-1. DRP-1 is
     a 42-kDa Ca(2+)/calmodulin (CaM)-regulated serine
```

threonine kinase which shows high degree of homology to DAP **kinase**. The region of homology spans the catalytic **domain** and the CaM-regulatory region, whereas the remaining **C-terminal** part of the protein differs completely from DAP **kinase** and displays no homology to any known protein. The catalytic **domain** is also homologous to the recently identified ZIP **kinase** and to a lesser extent to the catalytic **domains** of DRAK1 and -2. Thus, DAP **kinase DRP-1**, ZIP **kinase**, and DRAK1/2 together form a novel subfamily of **serine/threonine kinases**. **DRP-1** is localized to the cytoplasm, as shown by immunostaining and cellular fractionation assays. It binds to CaM, undergoes autophosphorylation, and phosphorylates an exogenous substrate, the myosin light chain, in a Ca(2+)/CaM-dependent manner. The truncated protein, deleted of the CaM-regulatory **domain**, was converted into a constitutively active **kinase**. Ectopically expressed **DRP-1** induced **apoptosis** in various types of cells. Cell killing by **DRP-1** was dependent on two features: the status of the catalytic activity, and the presence of the **C-terminal** 40 amino acids shown to be required for self-dimerization of the **kinase**. Interestingly, further deletion of the CaM-regulatory region could override the indispensable role of the **C-terminal** tail in **apoptosis** and generated a "superkiller" mutant. A dominant negative fragment of DAP **kinase** encompassing the death **domain** was found to block **apoptosis** induced by **DRP-1**. Conversely, a catalytically inactive mutant of **DRP-1**, which functioned in a dominant negative manner, was significantly less effective in blocking **cell death** induced by DAP **kinase** . Possible functional connections between DAP **kinase** and **DRP-1** are discussed.

CT Check Tags: Female; Human; Support, Non-U.S. Gov't
Amino Acid Sequence
***Apoptosis**
Base Sequence
Breast Neoplasms
Catalytic Domain
Cell Line
Cloning, Molecular
Gene Library
Kidney
Molecular Sequence Data
Phylogeny
***Protein-Serine-Threonine Kinases: CH, chemistry**
***Protein-Serine-Threonine Kinases: GE, genetics**
Protein-Serine-Threonine Kinases: ME, metabolism
RNA, Messenger: GE, genetics
Recombinant Proteins: CH, chemistry
Recombinant Proteins: ME, metabolism
Sequence Alignment
Sequence Homology, Amino Acid
Spleen: ME, metabolism
Transcription, Genetic
Translation, Genetic
Tumor Cells, Cultured

CN 0 (RNA, Messenger); 0 (Recombinant Proteins); EC 2.7.1.- (DRAK1 protein); EC 2.7.1.- (DRAK2 protein); EC 2.7.1.- (Protein-**Serine-Threonine Kinases**); EC 2.7.1.- (death-associated protein **kinase**-related protein 1)

=> d his

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     (FILE 'HOME' ENTERED AT 13:40:52 ON 05 JUN 2002)

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 13:41:17 ON 05 JUN 2002
L1             0 S CALMODULAIN
L2        110146 S CALMODULIN
L3        342878 S SERINE OR THREONINE
L4         73725 S L3 AND KINASE
L5          6021 S L2 AND L4
L6        422053 S (CELL (A) DEATH) OR APOPTOSIS
L7           391 S L5 AND L6
L8           195 S HUMAN AND L7
L9       1023024 S DOMAIN?
L10          111 S L7 AND L9
L11          345 S DAP(A)KINASE?
L12           72 S L10 AND L11
L13           23 DUP REM L12 (49 DUPLICATES REMOVED)
L14       255022 S CARBOXY(W) TERMINAL OR CARBOXY (W)END OR C-TERMINAL
L15           34 S L10 AND L14
L16           17 DUP REM L15 (17 DUPLICATES REMOVED)
L17        10019 S "DAP"
L18            6 S L16 AND L17
L19         4269 S "ZIP"
L20            2 S L16 AND L19
L21           98 S "DRP-1"
L22            1 S L16 AND L21

=> e kimchi a/au
E1             2     KIMCHE L/AU
E2             1     KIMCHE N/AU
E3           484 --> KIMCHI A/AU
E4             8     KIMCHI A */AU
E5             1     KIMCHI A N/AU
E6           131     KIMCHI ADI/AU
E7             1     KIMCHI ADY/AU
E8             5     KIMCHI B/AU
E9             2     KIMCHI BRACHA/AU
E10           24     KIMCHI D/AU
E11            1     KIMCHI DVORA/AU
E12           13     KIMCHI E/AU

=> s e3
L23          484 "KIMCHI A"/AU

=> s l16 and l23
L24            3 L16 AND L23

=> dup rem l24
PROCESSING COMPLETED FOR L24
L25            3 DUP REM L24 (0 DUPLICATES REMOVED)

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L25  ANSWER 1 OF 3     MEDLINE
ACCESSION NUMBER:   2001434353     MEDLINE
DOCUMENT NUMBER:    21214809   PubMed ID: 11313698
TITLE:              DAP-kinase: from functional gene cloning to
                    establishment of its role in apoptosis and
                    cancer.
AUTHOR:             Cohen O; Kimchi A
CORPORATE SOURCE:   Department of Molecular Genetics, Weizmann Institute of
```

Science, Rehovot 76100, Israel.
SOURCE: CELL DEATH AND DIFFERENTIATION, (2001 Jan) 8 (1) 6-15.
Ref: 39
Journal code: C7U; 9437445. ISSN: 1350-9047.
PUB. COUNTRY: England: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010806
Last Updated on STN: 20010806
Entered Medline: 20010802

AB DAP-**kinase** is a pro-apoptotic Ca(2+) **calmodulin**-regulated **serine/threonine kinase** that participates in a wide array of apoptotic systems initiated by interferon-gamma, TNF-alpha, activated Fas, and detachment from extracellular matrix. It was isolated by an unbiased functional approach to gene cloning aimed at hitting central mediators of the apoptotic process. This 160 Kd protein **kinase** is localized to actin microfilaments and carries interesting modules such as ankyrin repeats and the death **domain**. The death promoting effects of DAP-**kinase** depend on its intact catalytic activity, the correct intracellular localization, and on the presence of the death **domain**. A few mechanisms restrain the killing effects of the protein in healthy cells. The enzyme's active site is negatively controlled by an adjacent CaM regulatory **domain** whose effect is relieved by binding to Ca(2+)-activated **calmodulin**. A second mode of autoinhibition engages the **serine**-rich **C-terminal** tail, spanning the last 17 amino acids of the protein. A link between DAP-**kinase** and cancer has been established. It was found that the mRNA and protein expression is frequently lost in various human cancer cell lines. Analysis of the methylation status of DAP-**kinase**'s 5' UTR in DNA extracted from fresh tumor samples, showed high incidence of hypermethylation in several human carcinomas and B cell malignancies. The anti-tumorigenic effect of DAP-**kinase** was also studied experimentally in mouse model systems where the re-introduction of DAP-**kinase** into highly metastatic mouse lung carcinoma cells who had lost the protein, strongly reduced their metastatic capacity. Thus, it appears that loss of DAP-**kinase** confers a selective advantage to cancer cells and may play a causative role in tumor progression. A few novel **kinases** sharing high homology in their catalytic **domains** with DAP-**kinase** have been recently identified constituting altogether a novel family of death promoting **serine/threonine kinases**.

L25 ANSWER 2 OF 3 MEDLINE
ACCESSION NUMBER: 2000144081 MEDLINE
DOCUMENT NUMBER: 20144081 PubMed ID: 10677501
TITLE: A functional genetic screen identifies regions at the **C-terminal** tail and death-**domain** of death-associated protein **kinase** that are critical for its proapoptotic activity.
AUTHOR: Raveh T; Berissi H; Eisenstein M; Spivak T; **Kimchi A**
CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel.
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (2000 Feb 15) 97 (4) 1572-7.
Journal code: PV3; 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States

Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200003
ENTRY DATE: Entered STN: 20000330
Last Updated on STN: 20000330
Entered Medline: 20000323

AB Death-associated protein **kinase** (DAP-**kinase**) is a Ca(+2)/**calmodulin**-regulated **serine/threonine kinase** with a multidomain structure that participates in **apoptosis** induced by a variety of signals. To identify regions in this protein that are critical for its proapoptotic activity, we performed a genetic screen on the basis of functional selection of short DAP-**kinase**-derived fragments that could protect cells from **apoptosis** by acting in a dominant-negative manner. We expressed a library of randomly fragmented DAP-**kinase** cDNA in HeLa cells and treated these cells with IFN-gamma to induce **apoptosis**. Functional cDNA fragments were recovered from cells that survived the selection, and those in the sense orientation were examined further in a secondary screen for their ability to protect cells from DAP-**kinase**-dependent tumor necrosis factor-alpha-induced **apoptosis**. We isolated four biologically active peptides that mapped to the ankyrin repeats, the "linker" region, the death **domain**, and the **C-terminal** tail of DAP-**kinase**. Molecular modeling of the complete death **domain** provided a structural basis for the function of the death-**domain** -derived fragment by suggesting that the protective fragment constitutes a distinct substructure. The last fragment, spanning the **C-terminal serine**-rich tail, defined a new regulatory region. Ectopic expression of the tail peptide (17 amino acids) inhibited the function of DAP-**kinase**, whereas removal of this region from the complete protein caused enhancement of the killing activity, indicating that the **C-terminal** tail normally plays a negative regulatory role. Altogether, this unbiased screen highlighted functionally important regions in the protein and revealed an additional level of regulation of DAP-**kinase** apoptotic function that does not affect the catalytic activity.

L25 ANSWER 3 OF 3 MEDLINE
ACCESSION NUMBER: 2000094983 MEDLINE
DOCUMENT NUMBER: 20094983 PubMed ID: 10629061
TITLE: Death-associated protein **kinase**-related protein 1, a novel **serine/threonine kinase** involved in **apoptosis**.
AUTHOR: Inbal B; Shani G; Cohen O; Kissil J L; **Kimchi A**
CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel.
SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (2000 Feb) 20 (3) 1044-54. Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 20000229
Last Updated on STN: 20020420
Entered Medline: 20000214

AB In this study we describe the identification and structure-function analysis of a novel death-associated protein (DAP) **kinase** -related protein, DRP-1. DRP-1 is a 42-kDa Ca(2+)/**calmodulin** (CaM)-regulated **serine threonine kinase** which shows high degree of homology to DAP **kinase**. The region of

homology spans the catalytic **domain** and the CaM-regulatory region, whereas the remaining **C-terminal** part of the protein differs completely from DAP **kinase** and displays no homology to any known protein. The catalytic **domain** is also homologous to the recently identified ZIP **kinase** and to a lesser extent to the catalytic **domains** of DRAK1 and -2. Thus, DAP **kinase** DRP-1, ZIP **kinase**, and DRAK1/2 together form a novel subfamily of **serine/threonine kinases**.
DRP-1 is localized to the cytoplasm, as shown by immunostaining and cellular fractionation assays. It binds to CaM, undergoes autophosphorylation, and phosphorylates an exogenous substrate, the myosin light chain, in a Ca(2+)/CaM-dependent manner. The truncated protein, deleted of the CaM-regulatory **domain**, was converted into a constitutively active **kinase**. Ectopically expressed DRP-1 induced **apoptosis** in various types of cells. Cell killing by DRP-1 was dependent on two features: the status of the catalytic activity, and the presence of the **C-terminal** 40 amino acids shown to be required for self-dimerization of the **kinase**. Interestingly, further deletion of the CaM-regulatory region could override the indispensable role of the **C-terminal** tail in **apoptosis** and generated a "superkiller" mutant. A dominant negative fragment of DAP **kinase** encompassing the death **domain** was found to block **apoptosis** induced by DRP-1. Conversely, a catalytically inactive mutant of DRP-1, which functioned in a dominant negative manner, was significantly less effective in blocking **cell death** induced by DAP **kinase**. Possible functional connections between DAP **kinase** and DRP-1 are discussed.

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(FILE 'HOME' ENTERED AT 13:40:52 ON 05 JUN 2002)

FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS, LIFESCI' ENTERED AT 13:41:17 ON 05 JUN 2002

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L1             0 S CALMODULAIN
L2        110146 S CALMODULIN
L3        342878 S SERINE OR THREONINE
L4         73725 S L3 AND KINASE
L5          6021 S L2 AND L4
L6        422053 S (CELL (A) DEATH) OR APOPTOSIS
L7           391 S L5 AND L6
L8           195 S HUMAN AND L7
L9       1023024 S DOMAIN?
L10          111 S L7 AND L9
L11          345 S DAP(A)KINASE?
L12           72 S L10 AND L11
L13           23 DUP REM L12 (49 DUPLICATES REMOVED)
L14       255022 S CARBOXY(W) TERMINAL OR CARBOXY (W)END OR C-TERMINAL
L15           34 S L10 AND L14
L16           17 DUP REM L15 (17 DUPLICATES REMOVED)
L17        10019 S "DAP"
L18            6 S L16 AND L17
L19         4269 S "ZIP"
L20            2 S L16 AND L19
L21           98 S "DRP-1"
L22            1 S L16 AND L21
                 E KIMCHI A/AU
L23          484 S E3
L24            3 S L16 AND L23
L25            3 DUP REM L24 (0 DUPLICATES REMOVED)
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=> s l25 and drp##
L26 1 L25 AND DRP##

=> s l23 and drp##
L27 7 L23 AND DRP##

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L28 2 DUP REM L27 (5 DUPLICATES REMOVED)

=> d 1-2 ibib ab

L28 ANSWER 1 OF 2 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2001216755 MEDLINE
DOCUMENT NUMBER: 21153208 PubMed ID: 11230133
TITLE: Autophosphorylation restrains the apoptotic activity of **DRP**-1 kinase by controlling dimerization and calmodulin binding.
AUTHOR: Shani G; Henis-Korenblit S; Jona G; Gileadi O; Eisenstein M; Ziv T; Admon A; **Kimchi A**
CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel.
SOURCE: EMBO JOURNAL, (2001 Mar 1) 20 (5) 1099-113.
Journal code: 8208664. ISSN: 0261-4189.
PUB. COUNTRY: England: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200104
ENTRY DATE: Entered STN: 20010425
Last Updated on STN: 20020420
Entered Medline: 20010419

AB **DRP**-1 is a pro-apoptotic Ca2+/calmodulin (CaM)-regulated serine/threonine kinase, recently isolated as a novel member of the DAP-kinase family of proteins. It contains a short extra-catalytic tail required for homodimerization. Here we identify a novel regulatory mechanism that controls its pro-apoptotic functions. It comprises a single autophosphorylation event mapped to Ser308 within the CaM regulatory domain. A negative charge at this site reduces both the binding to CaM and the formation of **DRP**-1 homodimers. Conversely, the dephosphorylation of Ser308, which takes place in response to activated Fas or tumour necrosis factor-alpha death receptors, increases the formation of **DRP**-1 dimers, facilitates the binding to CaM and activates the pro-apoptotic effects of the protein. Thus, the process of enzyme activation is controlled by two unlocking steps that must work in concert, i.e. dephosphorylation, which probably weakens the electrostatic interactions between the CaM regulatory domain and the catalytic cleft, and homodimerization. This mechanism of negative autophosphorylation provides a safety barrier that restrains the killing effects of **DRP**-1, and a target for efficient activation of the kinase by various apoptotic stimuli.

L28 ANSWER 2 OF 2 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2000094983 MEDLINE
DOCUMENT NUMBER: 20094983 PubMed ID: 10629061
TITLE: Death-associated protein kinase-related protein 1, a novel serine/threonine kinase involved in apoptosis.
AUTHOR: Inbal B; Shani G; Cohen O; Kissil J L; **Kimchi A**
CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel.
SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (2000 Feb) 20 (3) 1044-54.

Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 20000229
Last Updated on STN: 20020420
Entered Medline: 20000214

AB In this study we describe the identification and structure-function analysis of a novel death-associated protein (DAP) kinase-related protein, **DRP**-1. **DRP**-1 is a 42-kDa Ca(2+)/calmodulin (CaM)-regulated serine threonine kinase which shows high degree of homology to DAP kinase. The region of homology spans the catalytic domain and the CaM-regulatory region, whereas the remaining C-terminal part of the protein differs completely from DAP kinase and displays no homology to any known protein. The catalytic domain is also homologous to the recently identified ZIP kinase and to a lesser extent to the catalytic domains of DRAK1 and -2. Thus, DAP kinase **DRP**-1, ZIP kinase, and DRAK1/2 together form a novel subfamily of serine/threonine kinases. **DRP** -1 is localized to the cytoplasm, as shown by immunostaining and cellular fractionation assays. It binds to CaM, undergoes autophosphorylation, and phosphorylates an exogenous substrate, the myosin light chain, in a Ca(2+)/CaM-dependent manner. The truncated protein, deleted of the CaM-regulatory domain, was converted into a constitutively active kinase. Ectopically expressed **DRP**-1 induced apoptosis in various types of cells. Cell killing by **DRP**-1 was dependent on two features: the status of the catalytic activity, and the presence of the C-terminal 40 amino acids shown to be required for self-dimerization of the kinase. Interestingly, further deletion of the CaM-regulatory region could override the indispensable role of the C-terminal tail in apoptosis and generated a "superkiller" mutant. A dominant negative fragment of DAP kinase encompassing the death domain was found to block apoptosis induced by **DRP**-1. Conversely, a catalytically inactive mutant of **DRP**-1, which functioned in a dominant negative manner, was significantly less effective in blocking cell death induced by DAP kinase. Possible functional connections between DAP kinase and **DRP**-1 are discussed.

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L3	342878	S	SERINE OR THREONINE
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L5	6021	S	L2 AND L4
L6	422053	S	(CELL (A) DEATH) OR APOPTOSIS
L7	391	S	L5 AND L6
L8	195	S	HUMAN AND L7
L9	1023024	S	DOMAIN?
L10	111	S	L7 AND L9
L11	345	S	DAP(A)KINASE?
L12	72	S	L10 AND L11
L13	23		DUP REM L12 (49 DUPLICATES REMOVED)
L14	255022	S	CARBOXY(W) TERMINAL OR CARBOXY (W)END OR C-TERMINAL
L15	34	S	L10 AND L14
L16	17		DUP REM L15 (17 DUPLICATES REMOVED)

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L17       10019 S "DAP"
L18           6 S L16 AND L17
L19        4269 S "ZIP"
L20           2 S L16 AND L19
L21          98 S "DRP-1"
L22           1 S L16 AND L21
                E KIMCHI A/AU
L23         484 S E3
L24           3 S L16 AND L23
L25           3 DUP REM L24 (0 DUPLICATES REMOVED)
L26           1 S L25 AND DRP##
L27           7 S L23 AND DRP##
L28           2 DUP REM L27 (5 DUPLICATES REMOVED)

=> s l23 and l17
L29          81 L23 AND L17

=> s l29 and l14
L30          18 L29 AND L14

=> dup rem l30
PROCESSING COMPLETED FOR L30
L31           6 DUP REM L30 (12 DUPLICATES REMOVED)

=> d 1-6 ibib ab

L31  ANSWER 1 OF 6  SCISEARCH  COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER:    2002:92210  SCISEARCH
THE GENUINE ARTICLE: 514CW
TITLE:               Death-associated protein (DAP) kinase plays a
                     central role in ceramide-induced apoptosis in cultured
                     hippocampal neurons
AUTHOR:              Pelled D; Raveh T; Riebeling C; Fridkin M; Berissi H;
                     Futerman A H (Reprint); Kimchi A
CORPORATE SOURCE:    Weizmann Inst Sci, Dept Biol Chem, IL-76100 Rehovot,
                     Israel (Reprint); Weizmann Inst Sci, Dept Mol Genet,
                     IL-76100 Rehovot, Israel; Weizmann Inst Sci, Dept Organ
                     Chem, IL-76100 Rehovot, Israel
COUNTRY OF AUTHOR:   Israel
SOURCE:              JOURNAL OF BIOLOGICAL CHEMISTRY, (18 JAN 2002) Vol. 277,
                     No. 3, pp. 1957-1961.
                     Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC,
                     9650 ROCKVILLE PIKE, BETHESDA, MD 20814 USA.
                     ISSN: 0021-9258.
DOCUMENT TYPE:       Article; Journal
LANGUAGE:            English
REFERENCE COUNT:     21
                    *ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*
AB       Treatment of cultured hippocampal neurons with high concentrations of
      short-chain acyl ceramide derivatives, such as N-hexanoyl-D-sphingosine
      (C-6-Cer), results in apoptotic cell death. We now show that
      death-associated protein (DAP) kinase plays an important role in
      mediating this effect. Upon incubation with C-6-Cer, DAP kinase
      levels are elevated as early as 1 h after treatment, reaching levels
      2-3-fold higher than untreated cells after 4 h. Neurons cultured from
      DAP kinase-deficient mice were significantly less sensitive to
      apoptosis induced by C-6-Cer or by ceramide generated by high
      concentrations of nerve growth factor. A peptide corresponding to the 17
      amino acids at the C terminus of DAP kinase protected wild type
      neurons from C-6-Cer-induced death and from death induced by the addition
      of exogenous bacterial neutral sphingomyelinase, whereas a scrambled
      peptide had no protective effect, implying that the DAP kinase
```

C-terminal tail inhibits the function of **DAP** kinase. Together, these data demonstrate that **DAP** kinase plays a central role in ceramide-induced cell death in neurons, but the pathway in which **DAP** kinase is involved is not the only one via which ceramide can induce apoptosis.

L31 ANSWER 2 OF 6 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2001434353 MEDLINE
DOCUMENT NUMBER: 21214809 PubMed ID: 11313698
TITLE: **DAP**-kinase: from functional gene cloning to establishment of its role in apoptosis and cancer.
AUTHOR: Cohen O; **Kimchi A**
CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel.
SOURCE: CELL DEATH AND DIFFERENTIATION, (2001 Jan) 8 (1) 6-15.
Ref: 39
Journal code: C7U; 9437445. ISSN: 1350-9047.
PUB. COUNTRY: England: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010806
Last Updated on STN: 20010806
Entered Medline: 20010802

AB **DAP**-kinase is a pro-apoptotic Ca(2+) calmodulin-regulated serine/threonine kinase that participates in a wide array of apoptotic systems initiated by interferon-gamma, TNF-alpha, activated Fas, and detachment from extracellular matrix. It was isolated by an unbiased functional approach to gene cloning aimed at hitting central mediators of the apoptotic process. This 160 Kd protein kinase is localized to actin microfilaments and carries interesting modules such as ankyrin repeats and the death domain. The death promoting effects of **DAP**-kinase depend on its intact catalytic activity, the correct intracellular localization, and on the presence of the death domain. A few mechanisms restrain the killing effects of the protein in healthy cells. The enzyme's active site is negatively controlled by an adjacent CaM regulatory domain whose effect is relieved by binding to Ca(2+)-activated calmodulin. A second mode of autoinhibition engages the serine-rich **C-terminal** tail, spanning the last 17 amino acids of the protein. A link between **DAP**-kinase and cancer has been established. It was found that the mRNA and protein expression is frequently lost in various human cancer cell lines. Analysis of the methylation status of **DAP**-kinase's 5' UTR in DNA extracted from fresh tumor samples, showed high incidence of hypermethylation in several human carcinomas and B cell malignancies. The anti-tumorigenic effect of **DAP**-kinase was also studied experimentally in mouse model systems where the re-introduction of **DAP**-kinase into highly metastatic mouse lung carcinoma cells who had lost the protein, strongly reduced their metastatic capacity. Thus, it appears that loss of **DAP**-kinase confers a selective advantage to cancer cells and may play a causative role in tumor progression. A few novel kinases sharing high homology in their catalytic domains with **DAP**-kinase have been recently identified constituting altogether a novel family of death promoting serine/threonine kinases.

L31 ANSWER 3 OF 6 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2000144081 MEDLINE
DOCUMENT NUMBER: 20144081 PubMed ID: 10677501
TITLE: A functional genetic screen identifies regions at the **C-terminal** tail and death-domain of

death-associated protein kinase that are critical for its proapoptotic activity.

AUTHOR: Raveh T; Berissi H; Eisenstein M; Spivak T; **Kimchi A**

CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel.

SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (2000 Feb 15) 97 (4) 1572-7. Journal code: PV3; 7505876. ISSN: 0027-8424.

PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200003

ENTRY DATE: Entered STN: 20000330
Last Updated on STN: 20000330
Entered Medline: 20000323

AB Death-associated protein kinase (**DAP**-kinase) is a Ca(+2)/calmodulin-regulated serine/threonine kinase with a multidomain structure that participates in apoptosis induced by a variety of signals. To identify regions in this protein that are critical for its proapoptotic activity, we performed a genetic screen on the basis of functional selection of short **DAP**-kinase-derived fragments that could protect cells from apoptosis by acting in a dominant-negative manner. We expressed a library of randomly fragmented **DAP**-kinase cDNA in HeLa cells and treated these cells with IFN-gamma to induce apoptosis. Functional cDNA fragments were recovered from cells that survived the selection, and those in the sense orientation were examined further in a secondary screen for their ability to protect cells from **DAP**-kinase-dependent tumor necrosis factor-alpha-induced apoptosis. We isolated four biologically active peptides that mapped to the ankyrin repeats, the "linker" region, the death domain, and the **C-terminal** tail of **DAP**-kinase. Molecular modeling of the complete death domain provided a structural basis for the function of the death-domain-derived fragment by suggesting that the protective fragment constitutes a distinct substructure. The last fragment, spanning the **C-terminal** serine-rich tail, defined a new regulatory region. Ectopic expression of the tail peptide (17 amino acids) inhibited the function of **DAP**-kinase, whereas removal of this region from the complete protein caused enhancement of the killing activity, indicating that the **C-terminal** tail normally plays a negative regulatory role. Altogether, this unbiased screen highlighted functionally important regions in the protein and revealed an additional level of regulation of **DAP**-kinase apoptotic function that does not affect the catalytic activity.

L31 ANSWER 4 OF 6 MEDLINE DUPLICATE 3

ACCESSION NUMBER: 2000094983 MEDLINE

DOCUMENT NUMBER: 20094983 PubMed ID: 10629061

TITLE: Death-associated protein kinase-related protein 1, a novel serine/threonine kinase involved in apoptosis.

AUTHOR: Inbal B; Shani G; Cohen O; Kissil J L; **Kimchi A**

CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel.

SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (2000 Feb) 20 (3) 1044-54. Journal code: 8109087. ISSN: 0270-7306.

PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200002

ENTRY DATE: Entered STN: 20000229

Last Updated on STN: 20020420
Entered Medline: 20000214

AB In this study we describe the identification and structure-function analysis of a novel death-associated protein (**DAP**) kinase-related protein, DRP-1. DRP-1 is a 42-kDa Ca(2+)/calmodulin (CaM)-regulated serine threonine kinase which shows high degree of homology to **DAP** kinase. The region of homology spans the catalytic domain and the CaM-regulatory region, whereas the remaining **C-terminal** part of the protein differs completely from **DAP** kinase and displays no homology to any known protein. The catalytic domain is also homologous to the recently identified ZIP kinase and to a lesser extent to the catalytic domains of DRAK1 and -2. Thus, **DAP** kinase DRP-1, ZIP kinase, and DRAK1/2 together form a novel subfamily of serine/threonine kinases. DRP-1 is localized to the cytoplasm, as shown by immunostaining and cellular fractionation assays. It binds to CaM, undergoes autophosphorylation, and phosphorylates an exogenous substrate, the myosin light chain, in a Ca(2+)/CaM-dependent manner. The truncated protein, deleted of the CaM-regulatory domain, was converted into a constitutively active kinase. Ectopically expressed DRP-1 induced apoptosis in various types of cells. Cell killing by DRP-1 was dependent on two features: the status of the catalytic activity, and the presence of the **C-terminal** 40 amino acids shown to be required for self-dimerization of the kinase. Interestingly, further deletion of the CaM-regulatory region could override the indispensable role of the **C-terminal** tail in apoptosis and generated a "superkiller" mutant. A dominant negative fragment of **DAP** kinase encompassing the death domain was found to block apoptosis induced by DRP-1. Conversely, a catalytically inactive mutant of DRP-1, which functioned in a dominant negative manner, was significantly less effective in blocking cell death induced by **DAP** kinase. Possible functional connections between **DAP** kinase and DRP-1 are discussed.

L31 ANSWER 5 OF 6 MEDLINE
ACCESSION NUMBER: 2000079262 MEDLINE
DOCUMENT NUMBER: 20079262 PubMed ID: 10611228
TITLE: A novel form of DAP5 protein accumulates in apoptotic cells as a result of caspase cleavage and internal ribosome entry site-mediated translation.
AUTHOR: Henis-Korenblit S; Strumpf N L; Goldstaub D; **Kimchi A**
CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel.
SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (2000 Jan) 20 (2) 496-506. Journal code: NGY; 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200001
ENTRY DATE: Entered STN: 20000204
Last Updated on STN: 20000204
Entered Medline: 20000127

AB Death-associated protein 5 (DAP5) (also named p97 and NAT1) is a member of the translation initiation factor 4G (eIF4G) family that lacks the eIF4E binding site. It was previously implicated in apoptosis, based on the finding that a dominant negative fragment of the protein protected against cell death. Here we address its function and two distinct levels of regulation during apoptosis that affect the protein both at translational and posttranslational levels. DAP5 protein was found to be cleaved at a single caspase cleavage site at position 790, in response to activated Fas or p53, yielding a **C-terminal** truncated protein of 86

kDa that is capable of generating complexes with eIF4A and eIF3. Interestingly, while the overall translation rate in apoptotic cells was reduced by 60 to 70%, in accordance with the simultaneous degradation of the two major mediators of cap-dependent translation, eIF4GI and eIF4GII, the translation rate of DAP5 protein was selectively maintained. An internal ribosome entry site (IRES) element capable of directing the translation of a reporter gene when subcloned into a bicistronic vector was identified in the 5' untranslated region of DAP5 mRNA. While cap-dependent translation from this transfected vector was reduced during Fas-induced apoptosis, the translation via the DAP5 IRES was selectively maintained. Addition of recombinant DAP5/p97 or DAP5/p86 to cell-free systems enhanced preferentially the translation through the DAP5 IRES, whereas neutralization of the endogenous DAP5 in reticulocyte lysates by adding a dominant negative DAP5 fragment interfered with this translation. The DAP5/p86 apoptotic form was more potent than DAP5/p97 in these functional assays. Altogether, the data suggest that DAP5 is a caspase-activated translation factor which mediates cap-independent translation at least from its own IRES, thus generating a positive feedback loop responsible for the continuous translation of DAP5 during apoptosis.

L31 ANSWER 6 OF 6 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 97184487 MEDLINE
DOCUMENT NUMBER: 97184487 PubMed ID: 9032289
TITLE: **DAP**-5, a novel homolog of eukaryotic translation initiation factor 4G isolated as a putative modulator of gamma interferon-induced programmed cell death.
AUTHOR: Levy-Strumpf N; Deiss L P; Berissi H; **Kimchi A**
CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot, Israel.
SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (1997 Mar) 17 (3) 1615-25. Journal code: NGY; 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-X89713
ENTRY MONTH: 199703
ENTRY DATE: Entered STN: 19970327
Last Updated on STN: 19970327
Entered Medline: 19970314

AB A functional approach to gene cloning was applied to HeLa cells in an attempt to isolate cDNA fragments which convey resistance to gamma interferon (IFN-gamma)-induced programmed cell death. One of the rescued cDNAs, described in this work, was a fragment of a novel gene, named **DAP**-5. Analysis of a **DAP**-5 full-length cDNA clone revealed that it codes for a 97-kDa protein that is highly homologous to eukaryotic translation initiation factor 4G (eIF4G, also known as p220). According to its deduced amino acid sequence, this novel protein lacks the N-terminal region of eIF4G responsible for association with the cap binding protein eIF4E. The N-terminal part of **DAP**-5 has 39% identity and 63% similarity to the central region of mammalian p220. Its **C-terminal** part is less homologous to the corresponding region of p220, suggesting that it may possess unique functional properties. The rescued **DAP**-5 cDNA fragment which conveyed resistance to IFN-gamma-induced cell death was expressed from the vector in the sense orientation. Intriguingly, it comprised part of the coding region which corresponds to the less conserved **C-terminal** part of **DAP**-5 and directed the synthesis of a 28-kDa miniprotein. The miniprotein exerted a dual effect on HeLa cells. Low levels of expression protected the cells from IFN-gamma-induced programmed cell death, while high levels of expression were not compatible

with continuous cell growth. The relevance of **DAP**-5 protein to possible changes in a cell's translational machinery during programmed cell death and growth arrest is discussed.

```
=> d his

     (FILE 'HOME' ENTERED AT 13:40:52 ON 05 JUN 2002)

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 13:41:17 ON 05 JUN 2002
L1             0 S CALMODULAIN
L2        110146 S CALMODULIN
L3        342878 S SERINE OR THREONINE
L4         73725 S L3 AND KINASE
L5          6021 S L2 AND L4
L6        422053 S (CELL (A) DEATH) OR APOPTOSIS
L7           391 S L5 AND L6
L8           195 S HUMAN AND L7
L9       1023024 S DOMAIN?
L10          111 S L7 AND L9
L11          345 S DAP(A)KINASE?
L12           72 S L10 AND L11
L13           23 DUP REM L12 (49 DUPLICATES REMOVED)
L14       255022 S CARBOXY(W) TERMINAL OR CARBOXY (W)END OR C-TERMINAL
L15           34 S L10 AND L14
L16           17 DUP REM L15 (17 DUPLICATES REMOVED)
L17        10019 S "DAP"
L18            6 S L16 AND L17
L19         4269 S "ZIP"
L20            2 S L16 AND L19
L21           98 S "DRP-1"
L22            1 S L16 AND L21
                 E KIMCHI A/AU
L23          484 S E3
L24            3 S L16 AND L23
L25            3 DUP REM L24 (0 DUPLICATES REMOVED)
L26            1 S L25 AND DRP##
L27            7 S L23 AND DRP##
L28            2 DUP REM L27 (5 DUPLICATES REMOVED)
L29           81 S L23 AND L17
L30           18 S L29 AND L14
L31            6 DUP REM L30 (12 DUPLICATES REMOVED)

=> s  l16 and regulat?
L32           15 L16 AND REGULAT?

=> dup rem l32
PROCESSING COMPLETED FOR L32
L33           15 DUP REM L32 (0 DUPLICATES REMOVED)

=> d 1-15 ibib ab

L33  ANSWER 1 OF 15  HCAPLUS  COPYRIGHT 2002 ACS
ACCESSION NUMBER:         2002:43345  HCAPLUS
DOCUMENT NUMBER:          136:319709
TITLE:                    Transcriptional profiling reveals global defects in
                          energy metabolism, lipoprotein, and bile acid
                          synthesis and transport with reversal by leptin
                          treatment in Ob/ob mouse liver
AUTHOR(S):                Liang, Chien-Ping; Tall, Alan R.
CORPORATE SOURCE:         Division of Molecular Medicine, Department of
```

Medicine, Columbia University, New York, NY, 10032, USA
SOURCE: Journal of Biological Chemistry (2001), 276(52), 49066-49076
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Leptin, a hormone secreted by adipose tissue, has been shown to have a major influence on hepatic lipid and lipoprotein metab. To characterize changes in lipid and lipoprotein gene expression in mouse liver, suppression subtractive hybridization and cDNA microarray anal. were used to identify mRNAs differentially expressed after leptin treatment of ob/ob mice. Ob/ob mice showed a profound decrease in mRNAs encoding genes controlling bile acid synthesis and transport as well as a variety of apolipoprotein genes and hepatic lipase with reversal upon leptin administration, suggesting that leptin coordinately **regulates** high d. lipoprotein and bile salt metab. Leptin administration also resulted in decreased expression of genes involved in fatty acid and cholesterol synthesis, glycolysis, gluconeogenesis, and urea synthesis, and increased expression of genes mediating fatty acid oxidn., ATP synthesis, and oxidant defenses. The changes in mRNA expression are consistent with a switch in energy metab. from glucose utilization and fatty acid synthesis to fatty acid oxidn. and increased respiration. The latter changes may produce oxidant stress, explaining the unexpected finding that leptin induces a battery of genes involved in antioxidant defenses. Expression cluster anal. revealed responses of several sets of genes that were kinetically linked. Thus, the mRNA levels of genes involved in fatty acid and cholesterol synthesis are rapidly (<1 h) repressed by leptin administration, in assocn. with an acute decrease in plasma insulin levels and decreased sterol **regulator** element-binding protein-1 expression. In contrast, genes participating in fatty acid oxidn. and ketogenesis were induced more slowly (24 h), following an increase in expression of their common **regulatory** factor, peroxisome proliferator-activated receptor .alpha.. However, the **regulation** of genes involved in high d. lipoprotein and bile salt metab. shows complex kinetics and is likely to be mediated by novel transcription factors.
REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 2 OF 15 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:775265 HCAPLUS
DOCUMENT NUMBER: 136:132090
TITLE: Investigation of differentially expressed genes during the development of mouse cerebellum
AUTHOR(S): Kagami, Yoshihiro; Furuichi, Teiichi
CORPORATE SOURCE: Laboratory for Molecular Neurogenesis, Brain Science Institute, RIKEN, Wako, 351-0198, Japan
SOURCE: Gene Expression Patterns (2001), 1(1), 39-59
CODEN: GEPEAD; ISSN: 1567-133X
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Before the discovery of DNA microarray and DNA chip technol., the expression of only a small no. of genes could be analyzed at a time. Currently, such technol. allows us the simultaneous anal. of a large no. of genes to systematically monitor their expression patterns that may be assocd. with various biol. phenomena. We utilized the Affymetrix GeneChip Mu11K to analyze the gene expression profile in developing mouse cerebellum to assist in the understanding of the genetic basis of

cerebellar development in mice. Our anal. showed 81.6% (10.321/12.654) of the genes represented on the GeneChip were expressed in the postnatal cerebellum, and among those, 8.7% (897/10.321) were differentially expressed with more than a two-fold change in their max. and min. expression levels during the developmental time course. Further anal. of the differentially expressed genes that were clustered in terms of their expression patterns and the function of their encoded products revealed an aspect of the genetic foundation that lies beneath the cellular events and neural network formation that takes place during the development of the mouse cerebellum.

REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 3 OF 15 MEDLINE
ACCESSION NUMBER: 2001434353 MEDLINE
DOCUMENT NUMBER: 21214809 PubMed ID: 11313698
TITLE: DAP-**kinase**: from functional gene cloning to establishment of its role in **apoptosis** and cancer.
AUTHOR: Cohen O; Kimchi A
CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel.
SOURCE: CELL DEATH AND DIFFERENTIATION, (2001 Jan) 8 (1) 6-15. Ref: 39
Journal code: C7U; 9437445. ISSN: 1350-9047.
PUB. COUNTRY: England: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010806
Last Updated on STN: 20010806
Entered Medline: 20010802

AB DAP-**kinase** is a pro-apoptotic Ca(2+) **calmodulin-regulated serine/threonine kinase** that participates in a wide array of apoptotic systems initiated by interferon-gamma, TNF-alpha, activated Fas, and detachment from extracellular matrix. It was isolated by an unbiased functional approach to gene cloning aimed at hitting central mediators of the apoptotic process. This 160 Kd protein **kinase** is localized to actin microfilaments and carries interesting modules such as ankyrin repeats and the death **domain**. The death promoting effects of DAP-**kinase** depend on its intact catalytic activity, the correct intracellular localization, and on the presence of the death **domain**. A few mechanisms restrain the killing effects of the protein in healthy cells. The enzyme's active site is negatively controlled by an adjacent CaM **regulatory domain** whose effect is relieved by binding to Ca(2+)-activated **calmodulin**. A second mode of autoinhibition engages the **serine**-rich **C-terminal** tail, spanning the last 17 amino acids of the protein. A link between DAP-**kinase** and cancer has been established. It was found that the mRNA and protein expression is frequently lost in various human cancer cell lines. Analysis of the methylation status of DAP-**kinase**'s 5' UTR in DNA extracted from fresh tumor samples, showed high incidence of hypermethylation in several human carcinomas and B cell malignancies. The anti-tumorigenic effect of DAP-**kinase** was also studied experimentally in mouse model systems where the re-introduction of DAP-**kinase** into highly metastatic mouse lung carcinoma cells who had lost the protein, strongly reduced their metastatic capacity. Thus, it appears that loss of DAP-**kinase**

confers a selective advantage to cancer cells and may play a causative role in tumor progression. A few novel **kinases** sharing high homology in their catalytic **domains** with DAP-**kinase** have been recently identified constituting altogether a novel family of death promoting **serine/threonine kinases**.

L33 ANSWER 4 OF 15 MEDLINE
ACCESSION NUMBER: 2000187596 MEDLINE
DOCUMENT NUMBER: 20187596 PubMed ID: 10722720
TITLE: Activation of MST/Krs and c-Jun N-terminal **kinases** by different signaling pathways during cytotrienin A-induced **apoptosis**.
AUTHOR: Watabe M; Kakeya H; Onose R; Osada H
CORPORATE SOURCE: Antibiotics Laboratory, RIKEN, 2-1 Hirosawa, Wako-shi, Saitama 351-0198, Japan.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2000 Mar 24) 275 (12) 8766-71.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200004
ENTRY DATE: Entered STN: 20000505
Last Updated on STN: 20020420
Entered Medline: 20000427

AB We found that antitumor drugs such as cytotrienin A, camptothecin, taxol, and 5-fluorouracil induced the activation of a 36-kDa protein **kinase** (p36 myelin basic protein (MBP) **kinase**) during **apoptosis** in human promyelocytic leukemia HL-60 cells. This p36 MBP **kinase**, which phosphorylates MBP in an in-gel **kinase** assay, results from the caspase-3-mediated proteolytic cleavage of MST/Krs protein, a mammalian Ste20-like **serine/threonine kinase**. Herein the correlation between cytotrienin A-induced **apoptosis** and the activation of MST/Krs proteins was examined in human tumor cell lines, including leukemia-, lung-, epidermoid-, cervix-, stomach-, and brain-derived cell lines. In cytotrienin A-sensitive cell lines, we observed a strong activation of p36 MBP **kinase** by cleavage of the **C-terminal regulatory domain** of full-length MST/Krs proteins by caspase-3. When the **kinase**-inactive mutant form of MST/Krs protein was overexpressed in cytotrienin A-sensitive HL-60 cells, the cytotrienin A-induced **apoptosis** was partially inhibited. Because cytotrienin A also activated c-Jun N-terminal **kinase**, we examined the effect of the expression of dominant negative c-Jun on cytotrienin A-induced **apoptosis**. The expression of dominant negative c-Jun also partially inhibited cytotrienin A-induced **apoptosis**. Furthermore, coexpression of **kinase**-inactive MST/Krs protein and dominant negative c-Jun completely suppressed cytotrienin A-induced **apoptosis**. These findings suggest that the proteolytic activation of MST/Krs and c-Jun N-terminal **kinase** activation are involved in cytotrienin A-induced **apoptosis** in human tumor cell lines.

L33 ANSWER 5 OF 15 MEDLINE
ACCESSION NUMBER: 2000144081 MEDLINE
DOCUMENT NUMBER: 20144081 PubMed ID: 10677501
TITLE: A functional genetic screen identifies regions at the **C-terminal** tail and death-**domain** of death-associated protein **kinase** that are critical for its proapoptotic activity.
AUTHOR: Raveh T; Berissi H; Eisenstein M; Spivak T; Kimchi A
CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of

Science, Rehovot 76100, Israel.
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (2000 Feb 15) 97 (4) 1572-7. Journal code: PV3; 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200003
ENTRY DATE: Entered STN: 20000330
Last Updated on STN: 20000330
Entered Medline: 20000323

AB Death-associated protein **kinase** (DAP-**kinase**) is a Ca(+2)/**calmodulin-regulated serine/threonine kinase** with a multidomain structure that participates in **apoptosis** induced by a variety of signals. To identify regions in this protein that are critical for its proapoptotic activity, we performed a genetic screen on the basis of functional selection of short DAP-**kinase**-derived fragments that could protect cells from **apoptosis** by acting in a dominant-negative manner. We expressed a library of randomly fragmented DAP-**kinase** cDNA in HeLa cells and treated these cells with IFN-gamma to induce **apoptosis**. Functional cDNA fragments were recovered from cells that survived the selection, and those in the sense orientation were examined further in a secondary screen for their ability to protect cells from DAP-**kinase**-dependent tumor necrosis factor-alpha-induced **apoptosis**. We isolated four biologically active peptides that mapped to the ankyrin repeats, the "linker" region, the death **domain**, and the **C-terminal** tail of DAP-**kinase**. Molecular modeling of the complete death **domain** provided a structural basis for the function of the death-**domain** -derived fragment by suggesting that the protective fragment constitutes a distinct substructure. The last fragment, spanning the **C-terminal serine**-rich tail, defined a new **regulatory** region. Ectopic expression of the tail peptide (17 amino acids) inhibited the function of DAP-**kinase**, whereas removal of this region from the complete protein caused enhancement of the killing activity, indicating that the **C-terminal** tail normally plays a negative **regulatory** role. Altogether, this unbiased screen highlighted functionally important regions in the protein and revealed an additional level of **regulation** of DAP-**kinase** apoptotic function that does not affect the catalytic activity.

L33 ANSWER 6 OF 15 MEDLINE
ACCESSION NUMBER: 2000094983 MEDLINE
DOCUMENT NUMBER: 20094983 PubMed ID: 10629061
TITLE: Death-associated protein **kinase**-related protein 1, a novel **serine/threonine kinase** involved in **apoptosis**.
AUTHOR: Inbal B; Shani G; Cohen O; Kissil J L; Kimchi A
CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel.
SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (2000 Feb) 20 (3) 1044-54. Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 20000229
Last Updated on STN: 20020420

Entered Medline: 20000214

AB In this study we describe the identification and structure-function analysis of a novel death-associated protein (DAP) **kinase**-related protein, DRP-1. DRP-1 is a 42-kDa Ca(2+)/**calmodulin** (CaM)-**regulated serine threonine kinase** which shows high degree of homology to DAP **kinase**. The region of homology spans the catalytic **domain** and the CaM-**regulatory** region, whereas the remaining **C-terminal** part of the protein differs completely from DAP **kinase** and displays no homology to any known protein. The catalytic **domain** is also homologous to the recently identified ZIP **kinase** and to a lesser extent to the catalytic **domains** of DRAK1 and -2. Thus, DAP **kinase** DRP-1, ZIP **kinase**, and DRAK1/2 together form a novel subfamily of **serine/threonine kinases**. DRP-1 is localized to the cytoplasm, as shown by immunostaining and cellular fractionation assays. It binds to CaM, undergoes autophosphorylation, and phosphorylates an exogenous substrate, the myosin light chain, in a Ca(2+)/CaM-dependent manner. The truncated protein, deleted of the CaM-**regulatory domain**, was converted into a constitutively active **kinase**. Ectopically expressed DRP-1 induced **apoptosis** in various types of cells. Cell killing by DRP-1 was dependent on two features: the status of the catalytic activity, and the presence of the **C-terminal** 40 amino acids shown to be required for self-dimerization of the **kinase**. Interestingly, further deletion of the CaM-**regulatory** region could override the indispensable role of the **C-terminal** tail in **apoptosis** and generated a "superkiller" mutant. A dominant negative fragment of DAP **kinase** encompassing the death **domain** was found to block **apoptosis** induced by DRP-1. Conversely, a catalytically inactive mutant of DRP-1, which functioned in a dominant negative manner, was significantly less effective in blocking **cell death** induced by DAP **kinase**. Possible functional connections between DAP **kinase** and DRP-1 are discussed.

L33 ANSWER 7 OF 15 MEDLINE
ACCESSION NUMBER: 2000481058 MEDLINE
DOCUMENT NUMBER: 20431384 PubMed ID: 10976872
TITLE: Activation of calcium/**calmodulin** **regulated kinases**.
AUTHOR: Wilmann M; Gautel M; Mayans O
CORPORATE SOURCE: EMBL, Hamburg, Germany.. wilmanns@embl-hamburg.de
SOURCE: CELLULAR AND MOLECULAR BIOLOGY, (2000 Jul) 46 (5) 883-94. Journal code: BNA; 9216789. ISSN: 0145-5680.
PUB. COUNTRY: France
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200010
ENTRY DATE: Entered STN: 20001019
Last Updated on STN: 20001019
Entered Medline: 20001012

AB Among numerous protein **kinases** found in mammalian cell systems there is a distinct subfamily of **serine/threonine kinases** that are **regulated** by **calmodulin** or other related activators in a calcium concentration dependent manner. Members of this family are involved in various cellular processes like cell proliferation and **death**, **cell** motility and metabolic pathways. In this contribution we shall review the available structural biology data on five members of this **kinase** family (calcium/**calmodulin** dependent **kinase**, twitchin **kinase**, titin **kinase**, phosphorylase **kinase**,

myosin light chain **kinase**). As a common element, all these **kinases** contain a **regulatory** tail, which is **C-terminal** to their catalytic **domain**. The available 3D structures of two members, the **serine/threonine kinases** of the giant muscle proteins twitchin and titin in the autoinhibited conformation, show how this **regulatory** tail blocks their active sites. The structures suggest that activation of these **kinases** requires unblocking the active site from the **C-terminal** extension and conformational rearrangement of the active site loops. Small angle scattering data for myosin light chain **kinase** indicate a complete release of the **C-terminal** extension upon calcium/**calmodulin** binding. In addition, members of this family are **regulated** by diverse add-on mechanisms, including phosphorylation of residues within the activation segment or the P+1 loop as well as by additional **regulatory** subunits. The available structural data lead to the hypothesis of two different activation mechanisms upon binding to calcium sensitive proteins. In one model, the **regulatory** tail is entirely released ("fall-apart"). The alternative model ("looping-out") proposes a two-anchored release mechanism.

L33 ANSWER 8 OF 15 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2000:430068 BIOSIS
DOCUMENT NUMBER: PREV200000430068
TITLE: Activation of calcium/**calmodulin regulated kinases**.
AUTHOR(S): Wilmanns, Mathias (1); Gautel, Mathias; Mayans, Olga
CORPORATE SOURCE: (1) EMBL c/o DESY, Notkestrasse 85, D-22603, Hamburg Germany
SOURCE: Cellular and Molecular Biology (Noisy-Le-Grand), (July, 2000) Vol. 46, No. 5, pp. 883-894. print.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Among numerous protein **kinases** found in mammalian cell systems there is a distinct subfamily of **serine/threonine kinases** that are **regulated** by **calmodulin** or other related activators in a calcium concentration dependent manner. Members of this family are involved in various cellular processes like cell proliferation and **death, cell** motility and metabolic pathways. In this contribution we shall review the available structural biology data on five members of this **kinase** family (calcium / **calmodulin** dependent **kinase**, twitchin **kinase**, titin **kinase**, phosphorylase **kinase**, myosin light chain **kinase**). As a common element, all these **kinases** contain a **regulatory** tail, which is **C-terminal** to their catalytic **domain**. The available 3D structures of two members, the **serine/threonine kinases** of the giant muscle protein twitchin and titin in the autoinhibited conformation, show how this **regulatory** tail blocks their active sites. The structures suggest that activation of these **kinases** requires unblocking the active site from the **C-terminal** extension and conformational rearrangement of the active site loops. Small angle scattering data for myosin light chain **kinase** indicate a complete release of the **C-terminal** extension upon calcium / **calmodulin** binding. In addition, members of this family are **regulated** by diverse add-on mechanisms, including phosphorylation of residues within the activation segment or the P+1 loop as well as by additional **regulatory** subunits. The available structural data lead to the hypothesis of two different activation mechanisms upon binding to calcium sensitive proteins. In one model, the **regulatory** tail is entirely released

("fall-apart"). The alternative model ("looping-out") proposes a two-anchored release mechanism.

L33 ANSWER 9 OF 15 MEDLINE
ACCESSION NUMBER: 1999430101 MEDLINE
DOCUMENT NUMBER: 99430101 PubMed ID: 10498871
TITLE: Requirement of protein **kinase** (Krs/MST) activation for MT-21-induced **apoptosis**.
AUTHOR: Watabe M; Kakeya H; Osada H
CORPORATE SOURCE: Laboratory of Antibiotics, The Institute of Physical and Chemical Research (RIKEN), 2-1 Hirosawa, Wako, Saitama 351-0198, Japan.
SOURCE: ONCOGENE, (1999 Sep 16) 18 (37) 5211-20. Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199910
ENTRY DATE: Entered STN: 19991101
Last Updated on STN: 20020420
Entered Medline: 19991021

AB Fas is a well characterized **apoptosis**-inducing factor. One of our synthetic compounds, MT-21, induced **apoptosis** in human leukemia HL-60 cells similar to Fas. MT-21 activated caspase-3, an important cysteine aspartic protease for **apoptosis** induction. MT-21 also activated c-Jun-NH2-terminal **kinase** (JNK), a member of mitogen activated protein **kinase** (MAPK) superfamily that is involved in the **regulation** of cell growth, differentiation and **cell death**. Moreover, MT-21 treatment resulted in the activation of a 36 kDa **kinase** which uses myelin basic protein (MBP) as a substrate. However, MAPK and p38 were not activated by treatment with MT-21. The 36 kDa MBP **kinase** was shown to be a proteolytic product derived from the Krs protein with a molecular weight of 60 kDa. The Krs protein is a Ser/Thr protein **kinase** whose activity is enhanced by digestion of its **C-terminal regulatory domain** by caspase-3. When a **kinase** -inactive mutant form of Krs protein was overexpressed in HL-60 cells, JNK activation and **apoptosis** induction by MT-21 were suppressed. Furthermore, overexpression of dominant negative c-Jun also suppressed **apoptosis** induction by MT-21. These findings indicate that MT-21 induces **apoptosis** by the activation of JNK via the Krs protein, which is activated by caspase cleavage.

L33 ANSWER 10 OF 15 MEDLINE
ACCESSION NUMBER: 1999164089 MEDLINE
DOCUMENT NUMBER: 99164089 PubMed ID: 10064589
TITLE: **Apoptosis** inhibitory activity of cytoplasmic p21(Cip1/WAF1) in monocytic differentiation.
AUTHOR: Asada M; Yamada T; Ichijo H; Delia D; Miyazono K; Fukumuro K; Mizutani S
CORPORATE SOURCE: Department of Virology, The National Children's Medical Research Center, 3-35-31, Taishido, Setagaya-ku, Tokyo, 154, Japan.
SOURCE: EMBO JOURNAL, (1999 Mar 1) 18 (5) 1223-34. Journal code: EMB; 8208664. ISSN: 0261-4189.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199904
ENTRY DATE: Entered STN: 19990511

Last Updated on STN: 20000303
Entered Medline: 19990429

AB p21(Cip1/WAF1) inhibits cell-cycle progression by binding to G1 cyclin/CDK complexes and proliferating cell nuclear antigen (PCNA) through its N- and **C-terminal domains**, respectively. The cell-cycle inhibitory activity of p21(Cip1/WAF1) is correlated with its nuclear localization. Here, we report a novel cytoplasmic localization of p21(Cip1/WAF1) in peripheral blood monocytes (PBMs) and in U937 cells undergoing monocytic differentiation by in vitro treatment with vitamin D3 or ectopic expression of p21(Cip1/WAF1), and analyze the biological consequences of this cytoplasmic expression. U937 cells which exhibit nuclear p21(Cip1/WAF1) demonstrated G1 cell-cycle arrest and subsequently differentiated into monocytes. The latter event was associated with a cytoplasmic expression of nuclear p21(Cip1/WAF1), concomitantly with a resistance to various apoptogenic stimuli. Biochemical analysis showed that cytoplasmic p21(Cip1/WAF1) forms a complex with the **apoptosis** signal-**regulating kinase** 1 (ASK1) and inhibits stress-activated MAP **kinase** cascade. Expression of a deletion mutant of p21(Cip1/WAF1) lacking the nuclear localization signal (DeltaNLS-p21) did not induce cell cycle arrest nor monocytic differentiation, but led to an **apoptosis**-resistant phenotype, mediated by binding to and inhibition of the stress-activated ASK1 activity. Thus, cytoplasmic p21(Cip1/WAF1) itself acted as an inhibitor of **apoptosis**. Our findings highlight the different functional roles of p21(Cip1/WAF1), which are determined by its intracellular distribution and are dependent on the stage of differentiation.

L33 ANSWER 11 OF 15 MEDLINE
ACCESSION NUMBER: 2000029738 MEDLINE
DOCUMENT NUMBER: 20029738 PubMed ID: 10561491
TITLE: Hematopoietic lineage cell specific protein 1 associates with and down-**regulates** protein **kinase** CK2.
AUTHOR: Ruzzene M; Brunati A M; Sarno S; Donella-Deana A; Pinna L A
CORPORATE SOURCE: Dipartimento di Chimica Biologica and Centro per lo Studio delle Biomembrane del CNR, University of Padova, Viale G. Colombo, 335121, Padova, Italy.
SOURCE: FEBS LETTERS, (1999 Nov 12) 461 (1-2) 32-6.
Journal code: 0155157. ISSN: 0014-5793.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199912
ENTRY DATE: Entered STN: 20000113
Last Updated on STN: 20020420
Entered Medline: 19991214

AB The catalytic (alpha) subunit of protein **kinase** CK2 and the hematopoietic specific protein 1 (HS1) display opposite effects on Ha-ras induced fibroblast transformation, by enhancing and counteracting it, respectively. Here we show the occurrence of physical association between HS1 and CK2alpha as judged from both far Western blot and plasmon resonance (BIAcore) analysis. Association of HS1 with CK2alpha is drastically reduced by the deletion of the HS1 **C-terminal** region (403-486) containing an SH3 **domain**. HS1, but not its deletion mutant HS1 Delta324-393, lacking a sequence similar to an acidic stretch of the **regulatory** beta-subunit of CK2, inhibits **calmodulin** phosphorylation by CK2alpha. These data indicate that HS1 physically interacts with CK2alpha and down-**regulates** its activity by a mechanism similar to the beta-subunit.

L33 ANSWER 12 OF 15 MEDLINE

ACCESSION NUMBER: 1999003259 MEDLINE
DOCUMENT NUMBER: 99003259 PubMed ID: 9786912
TITLE: DRAKs, novel **serine/threonine kinases** related to death-associated protein **kinase** that trigger **apoptosis**.
AUTHOR: Sanjo H; Kawai T; Akira S
CORPORATE SOURCE: Department of Biochemistry, Hyogo College of Medicine, 1-1 Mukogawa-cho, Nishinomiya, Hyogo 663-8501, Japan.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1998 Oct 30) 273 (44) 29066-71.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AB011420; GENBANK-AB011421
ENTRY MONTH: 199812
ENTRY DATE: Entered STN: 19990115
Last Updated on STN: 20020420
Entered Medline: 19981201

AB The present study describes the cloning of two novel **serine/threonine kinases** termed DRAK1 and DRAK2, whose catalytic **domains** are related to that of death-associated protein **kinase**, a **serine/threonine kinase** involved in **apoptosis**. Both DRAKs are composed of the N-terminal catalytic **domain** and the **C-terminal domain** that is responsible for **regulation** of **kinase** activity. DRAK1 and DRAK2 show 59.7% identity and display ubiquitous expression. An in vitro **kinase** assay revealed that both DRAKs are autophosphorylated and phosphorylate myosin light chain as an exogenous substrate, although the **kinase** activity of DRAK2 is significantly lower than that of DRAK1. Both DRAKs are exclusively localized to the nucleus. Furthermore, overexpression of both DRAKs induces the morphological changes of **apoptosis** in NIH 3T3 cells, suggesting the role of DRAKs in apoptotic signaling.

L33 ANSWER 13 OF 15 MEDLINE
ACCESSION NUMBER: 1998211933 MEDLINE
DOCUMENT NUMBER: 98211933 PubMed ID: 9545236
TITLE: Caspase-mediated activation and induction of **apoptosis** by the mammalian Ste20-like **kinase** Mst1.
AUTHOR: Graves J D; Gotoh Y; Draves K E; Ambrose D; Han D K; Wright M; Chernoff J; Clark E A; Krebs E G
CORPORATE SOURCE: Department of Immunology, University of Washington Medical Center, Seattle, WA 98109, USA.
CONTRACT NUMBER: GM37905 (NIGMS)
GM42508 (NIGMS)
SOURCE: EMBO JOURNAL, (1998 Apr 15) 17 (8) 2224-34.
Journal code: 8208664. ISSN: 0261-4189.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199806
ENTRY DATE: Entered STN: 19980708
Last Updated on STN: 20020420
Entered Medline: 19980624

AB Mst1 is a ubiquitously expressed **serine-threonine kinase**, homologous to the budding yeast Ste20, whose physiological **regulation** and cellular function are unknown. In this paper we

show that Mst1 is specifically cleaved by a caspase 3-like activity during **apoptosis** induced by either cross-linking CD95/Fas or by staurosporine treatment. CD95/Fas-induced cleavage of Mst1 was blocked by the cysteine protease inhibitor ZVAD-fmk, the more selective caspase inhibitor DEVD-CHO and by the viral serpin CrmA. Caspase-mediated cleavage of Mst1 removes the **C-terminal regulatory domain** and correlates with an increase in Mst1 activity in vivo, consistent with caspase-mediated cleavage activating Mst1. Overexpression of either wild-type Mst1 or a truncated mutant induces morphological changes characteristic of **apoptosis**. Furthermore, exogenously expressed Mst1 is cleaved, indicating that Mst1 can activate caspases that result in its cleavage. **Kinase**-dead Mst1 did not induce morphological alterations and was not cleaved upon overexpression, indicating that Mst1 must be catalytically active in order to mediate these effects. Mst1 activates MKK6, p38 MAPK, MKK7 and SAPK in co-transfection assays, suggesting that Mst1 may activate these pathways. Our findings suggest the existence of a positive feedback loop involving Mst1, and possibly the SAPK and p38 MAPK pathways, which serves to amplify the apoptotic response.

L33 ANSWER 14 OF 15 MEDLINE
ACCESSION NUMBER: 1998416694 MEDLINE
DOCUMENT NUMBER: 98416694 PubMed ID: 9739089
TITLE: Crystal structure of JNK3: a **kinase** implicated in neuronal **apoptosis**.
AUTHOR: Xie X; Gu Y; Fox T; Coll J T; Fleming M A; Markland W; Caron P R; Wilson K P; Su M S
CORPORATE SOURCE: Vertex Pharmaceuticals Incorporated, Cambridge, MA 02139-4211, USA.
SOURCE: STRUCTURE, (1998 Aug 15) 6 (8) 983-91.
Journal code: B31; 9418985. ISSN: 0969-2126.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: PDB-1JNK
ENTRY MONTH: 199812
ENTRY DATE: Entered STN: 19990115
Last Updated on STN: 20000303
Entered Medline: 19981208

AB BACKGROUND: The c-Jun N-terminal **kinases** (JNKs) are members of the mitogen-activated protein (MAP) **kinase** family, and **regulate** signal transduction in response to environmental stress. Activation and nuclear localization of JNK3, a neuronal-specific isoform of JNK, has been associated with hypoxic and ischemic damage of CA1 neurons in the hippocampus. Knockout mice lacking JNK3 showed reduced **apoptosis** of hippocampal neurons and reduced seizure induced by kainic acid, a glutamate-receptor agonist. Thus, JNK3 may be important in the pathology of neurological disorders and is of significant medical interest. RESULTS: We report here the structure of unphosphorylated JNK3 in complex with adenylyl imidodiphosphate, an ATP analog. JNK3 has a typical **kinase** fold, with the ATP-binding site situated within a cleft between the N- and **C-terminal domains**. In contrast to other known MAP **kinase** structures, the ATP-binding site of JNK3 is well ordered; the glycine-rich nucleotide-binding sequence forms a beta-strand-turn-beta-strand structure over the nucleotide. Unphosphorylated JNK3 assumes an open conformation, in which the N- and **C-terminal domains** are twisted apart relative to their positions in cAMP-dependent protein **kinase**. The rotation leads to the misalignment of some of the catalytic residues. The phosphorylation lip of JNK3 partially blocks the substrate-binding site. CONCLUSIONS: This is the first JNK structure to be

determined, providing a unique opportunity to compare structures from the three MAP **kinase** subfamilies. The structure reveals atomic-level details of the shape of JNK3 and the interactions between the **kinase** and the nucleotide. The misalignment of catalytic residues and occlusion of the active site by the phosphorylation lip may account for the low activity of unphosphorylated JNK3. The structure provides a framework for understanding the substrate specificity of different JNK isoforms, and should aid the design of selective JNK3 inhibitors.

L33 ANSWER 15 OF 15 MEDLINE
ACCESSION NUMBER: 97474480 MEDLINE
DOCUMENT NUMBER: 97474480 PubMed ID: 9335504
TITLE: Opposing BMP and EGF signalling pathways converge on the TGF-beta family mediator Smad1.
AUTHOR: Kretzschmar M; Doody J; Massague J
CORPORATE SOURCE: Cell Biology and Genetics Program, Memorial Sloan-Kettering Cancer Center, New York, New York 10021, USA.
SOURCE: NATURE, (1997 Oct 9) 389 (6651) 618-22.
Journal code: NSC; 0410462. ISSN: 0028-0836.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199711
ENTRY DATE: Entered STN: 19971224
Last Updated on STN: 20000303
Entered Medline: 19971103

AB The growth factor TGF-beta, bone morphogenetic proteins (BMPs) and related factors **regulate** cell proliferation, differentiation and **apoptosis**, controlling the development and maintenance of most tissues. Their signals are transmitted through the phosphorylation of the tumour-suppressor SMAD proteins by receptor protein **serine/threonine kinases** (RS/TKs), leading to the nuclear accumulation and transcriptional activity of SMAD proteins. Here we report that Smad1, which mediates BMP signals, is also a target of mitogenic growth-factor signalling through epidermal growth factor and hepatocyte growth factor receptor protein tyrosine **kinases** (RTKs). Phosphorylation occurs at specific **serines** within the region linking the inhibitory and effector **domains** of Smad1, and is catalysed by the Erk family of mitogen-activated protein **kinases**. In contrast to the BMP-stimulated phosphorylation of Smad1, which affects **carboxy-terminal serines** and induces nuclear accumulation of Smad1, Erk-mediated phosphorylation specifically inhibits the nuclear accumulation of Smad1. Thus, Smad1 receives opposing **regulatory** inputs through RTKs and RS/TKs, and it is this balance that determines the level of Smad1 activity in the nucleus, and so possibly the role of Smad1 in the control of cell fate.

=> d his

(FILE 'HOME' ENTERED AT 13:40:52 ON 05 JUN 2002)

FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS, LIFESCI' ENTERED AT 13:41:17 ON 05 JUN 2002

L1	0	S	CALMODULAIN
L2	110146	S	CALMODULIN
L3	342878	S	SERINE OR THREONINE
L4	73725	S	L3 AND KINASE
L5	6021	S	L2 AND L4
L6	422053	S	(CELL (A) DEATH) OR APOPTOSIS
L7	391	S	L5 AND L6

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L8          195 S HUMAN AND L7
L9      1023024 S DOMAIN?
L10         111 S L7 AND L9
L11         345 S DAP(A)KINASE?
L12          72 S L10 AND L11
L13          23 DUP REM L12 (49 DUPLICATES REMOVED)
L14      255022 S CARBOXY(W) TERMINAL OR CARBOXY (W)END OR C-TERMINAL
L15          34 S L10 AND L14
L16          17 DUP REM L15 (17 DUPLICATES REMOVED)
L17       10019 S "DAP"
L18           6 S L16 AND L17
L19        4269 S "ZIP"
L20           2 S L16 AND L19
L21          98 S "DRP-1"
L22           1 S L16 AND L21
                E KIMCHI A/AU
L23         484 S E3
L24           3 S L16 AND L23
L25           3 DUP REM L24 (0 DUPLICATES REMOVED)
L26           1 S L25 AND DRP##
L27           7 S L23 AND DRP##
L28           2 DUP REM L27 (5 DUPLICATES REMOVED)
L29          81 S L23 AND L17
L30          18 S L29 AND L14
L31           6 DUP REM L30 (12 DUPLICATES REMOVED)
L32          15 S  L16 AND REGULAT?
L33          15 DUP REM L32 (0 DUPLICATES REMOVED)

=> s "death domain?"
L34        3919 "DEATH DOMAIN?"

=> s l15 and l34
L35          19 L15 AND L34

=> dup rem l35
PROCESSING COMPLETED FOR L35
L36           5 DUP REM L35 (14 DUPLICATES REMOVED)

=> d 1-5 ibib ab

L36  ANSWER 1 OF 5  SCISEARCH  COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER:    2002:89428  SCISEARCH
THE GENUINE ARTICLE: 513UP
TITLE:               DAP kinase activity is critical for
                     C-2-ceramide-induced apoptosis in PC12 cells
AUTHOR:              Yamamoto M (Reprint); Hioki T; Ishii T; Nakajima-Iijima S;
                     Uchino S
CORPORATE SOURCE:    Mitsubishi Tokyo Pharmaceut Inc, Yokohama Res Ctr,
                     Pharmaceut Discovery Lab, Aoba Ku, 1000 Kamoshida,
                     Yokohama, Kanagawa 2278502, Japan (Reprint); Mitsubishi
                     Tokyo Pharmaceut Inc, Yokohama Res Ctr, Pharmaceut
                     Discovery Lab, Aoba Ku, Yokohama, Kanagawa 2278502, Japan
COUNTRY OF AUTHOR:   Japan
SOURCE:              EUROPEAN JOURNAL OF BIOCHEMISTRY, (JAN 2002) Vol. 269, No.
                     1, pp. 139-147.
                     Publisher: BLACKWELL SCIENCE LTD, P O BOX 88, OSNEY MEAD,
                     OXFORD OX2 0NE, OXON, ENGLAND.
                     ISSN: 0014-2956.
DOCUMENT TYPE:       Article; Journal
LANGUAGE:            English
REFERENCE COUNT:     41
                    *ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*
```

AB Exposure of PC12 cells to C-2-ceramide results in dose-dependent **apoptosis**. Here, we investigate the involvement of death-associated protein (DAP) **kinase**, initially identified as a positive mediator of the interferon-gamma-induced **apoptosis** of HeLa cells, in the C-2-ceramide-induced **apoptosis** of PC 12 cells. DAP **kinase** is endogenously expressed in these cells. On exposure of PC 12 cells to 30 muM C-2-ceramide, both the total (assayed in the presence of Ca2+/**calmodulin**) and Ca2+/**calmodulin** -independent (assayed in the presence of EGTA) DAP **kinase** activities were transiently increased 5.0- and 12.2-fold, respectively, at 10 min, and then decreased to 1.7- and 3.4-fold at 90 min. After 10 min exposure to 30 mum C-2-ceramide, the Ca2+/**calmodulin** independent activity/total activity ratio increased from 0.22 to 0.60. These effects were dependent on the C-2-ceramide concentration. C-8-ceramide, another active ceramide analog, also induced **apoptosis** and activated DAP **kinase**, while C-2-dihydroceramide, an inactive ceramide analog, failed to induce **apoptosis** and increase DAP **kinase** activity. Furthermore, transfection studies revealed that overexpression of wild-type DAP **kinase** enhanced the sensitivity to C-2- and C-8-ceramide, while a catalytically inactive DAP **kinase** mutant and a construct containing the **death domain** and **C-terminal** tail of DAP **kinase**, which act in a dominant-negative manner, rescued cells from C-2-, and C-8-ceramide-induced **apoptosis**. These findings demonstrate that DAP **kinase** is an important component of the apoptotic machinery involved in ceramide-induced **apoptosis**, and that the intrinsic DAP **kinase** activity is critical for ceramide-induced **apoptosis**.

L36 ANSWER 2 OF 5 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:43345 HCAPLUS
DOCUMENT NUMBER: 136:319709
TITLE: Transcriptional profiling reveals global defects in energy metabolism, lipoprotein, and bile acid synthesis and transport with reversal by leptin treatment in Ob/ob mouse liver
AUTHOR(S): Liang, Chien-Ping; Tall, Alan R.
CORPORATE SOURCE: Division of Molecular Medicine, Department of Medicine, Columbia University, New York, NY, 10032, USA
SOURCE: Journal of Biological Chemistry (2001), 276(52), 49066-49076
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Leptin, a hormone secreted by adipose tissue, has been shown to have a major influence on hepatic lipid and lipoprotein metab. To characterize changes in lipid and lipoprotein gene expression in mouse liver, suppression subtractive hybridization and cDNA microarray anal. were used to identify mRNAs differentially expressed after leptin treatment of ob/ob mice. Ob/ob mice showed a profound decrease in mRNAs encoding genes controlling bile acid synthesis and transport as well as a variety of apolipoprotein genes and hepatic lipase with reversal upon leptin administration, suggesting that leptin coordinately regulates high d. lipoprotein and bile salt metab. Leptin administration also resulted in decreased expression of genes involved in fatty acid and cholesterol synthesis, glycolysis, gluconeogenesis, and urea synthesis, and increased expression of genes mediating fatty acid oxidn., ATP synthesis, and oxidant defenses. The changes in mRNA expression are consistent with a switch in energy metab. from glucose utilization and fatty acid synthesis

to fatty acid oxidn. and increased respiration. The latter changes may produce oxidant stress, explaining the unexpected finding that leptin induces a battery of genes involved in antioxidant defenses. Expression cluster anal. revealed responses of several sets of genes that were kinetically linked. Thus, the mRNA levels of genes involved in fatty acid and cholesterol synthesis are rapidly (<1 h) repressed by leptin administration, in assocn. with an acute decrease in plasma insulin levels and decreased sterol regulator element-binding protein-1 expression. In contrast, genes participating in fatty acid oxidn. and ketogenesis were induced more slowly (24 h), following an increase in expression of their common regulatory factor, peroxisome proliferator-activated receptor .alpha.. However, the regulation of genes involved in high d. lipoprotein and bile salt metab. shows complex kinetics and is likely to be mediated by novel transcription factors.

REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 3 OF 5 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2001434353 MEDLINE
DOCUMENT NUMBER: 21214809 PubMed ID: 11313698
TITLE: DAP-**kinase**: from functional gene cloning to establishment of its role in **apoptosis** and cancer.
AUTHOR: Cohen O; Kimchi A
CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel.
SOURCE: CELL DEATH AND DIFFERENTIATION, (2001 Jan) 8 (1) 6-15. Ref: 39
Journal code: C7U; 9437445. ISSN: 1350-9047.
PUB. COUNTRY: England: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010806
Last Updated on STN: 20010806
Entered Medline: 20010802

AB DAP-**kinase** is a pro-apoptotic Ca(2+) **calmodulin**-regulated **serine/threonine kinase** that participates in a wide array of apoptotic systems initiated by interferon-gamma, TNF-alpha, activated Fas, and detachment from extracellular matrix. It was isolated by an unbiased functional approach to gene cloning aimed at hitting central mediators of the apoptotic process. This 160 Kd protein **kinase** is localized to actin microfilaments and carries interesting modules such as ankyrin repeats and the **death domain**. The death promoting effects of DAP-**kinase** depend on its intact catalytic activity, the correct intracellular localization, and on the presence of the **death domain**. A few mechanisms restrain the killing effects of the protein in healthy cells. The enzyme's active site is negatively controlled by an adjacent CaM regulatory **domain** whose effect is relieved by binding to Ca(2+)-activated **calmodulin**. A second mode of autoinhibition engages the **serine**-rich **C-terminal** tail, spanning the last 17 amino acids of the protein. A link between DAP-**kinase** and cancer has been established. It was found that the mRNA and protein expression is frequently lost in various human cancer cell lines. Analysis of the methylation status of DAP-**kinase**'s 5' UTR in DNA extracted from fresh tumor samples, showed high incidence of hypermethylation in several human carcinomas and B cell malignancies. The anti-tumorigenic effect of DAP-**kinase** was also

studied experimentally in mouse model systems where the re-introduction of DAP-**kinase** into highly metastatic mouse lung carcinoma cells who had lost the protein, strongly reduced their metastatic capacity. Thus, it appears that loss of DAP-**kinase** confers a selective advantage to cancer cells and may play a causative role in tumor progression. A few novel **kinases** sharing high homology in their catalytic **domains** with DAP-**kinase** have been recently identified constituting altogether a novel family of death promoting **serine /threonine kinases**.

L36 ANSWER 4 OF 5 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2000144081 MEDLINE
DOCUMENT NUMBER: 20144081 PubMed ID: 10677501
TITLE: A functional genetic screen identifies regions at the **C-terminal** tail and **death-domain** of death-associated protein **kinase** that are critical for its proapoptotic activity.
AUTHOR: Raveh T; Berissi H; Eisenstein M; Spivak T; Kimchi A
CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel.
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (2000 Feb 15) 97 (4) 1572-7. Journal code: PV3; 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200003
ENTRY DATE: Entered STN: 20000330
Last Updated on STN: 20000330
Entered Medline: 20000323

AB Death-associated protein **kinase** (DAP-**kinase**) is a Ca(+2)/**calmodulin**-regulated **serine/threonine kinase** with a multidomain structure that participates in **apoptosis** induced by a variety of signals. To identify regions in this protein that are critical for its proapoptotic activity, we performed a genetic screen on the basis of functional selection of short DAP-**kinase**-derived fragments that could protect cells from **apoptosis** by acting in a dominant-negative manner. We expressed a library of randomly fragmented DAP-**kinase** cDNA in HeLa cells and treated these cells with IFN-gamma to induce **apoptosis**. Functional cDNA fragments were recovered from cells that survived the selection, and those in the sense orientation were examined further in a secondary screen for their ability to protect cells from DAP-**kinase**-dependent tumor necrosis factor-alpha-induced **apoptosis**. We isolated four biologically active peptides that mapped to the ankyrin repeats, the "linker" region, the **death domain**, and the **C-terminal** tail of DAP-**kinase**. Molecular modeling of the complete **death domain** provided a structural basis for the function of the **death-domain**-derived fragment by suggesting that the protective fragment constitutes a distinct substructure. The last fragment, spanning the **C-terminal serine** -rich tail, defined a new regulatory region. Ectopic expression of the tail peptide (17 amino acids) inhibited the function of DAP-**kinase** , whereas removal of this region from the complete protein caused enhancement of the killing activity, indicating that the **C-terminal** tail normally plays a negative regulatory role. Altogether, this unbiased screen highlighted functionally important regions in the protein and revealed an additional level of regulation of DAP-**kinase** apoptotic function that does not affect the catalytic activity.

L36 ANSWER 5 OF 5 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 2000094983 MEDLINE
DOCUMENT NUMBER: 20094983 PubMed ID: 10629061
TITLE: Death-associated protein **kinase**-related protein 1, a novel **serine/threonine kinase** involved in **apoptosis**.
AUTHOR: Inbal B; Shani G; Cohen O; Kissil J L; Kimchi A
CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel.
SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (2000 Feb) 20 (3) 1044-54. Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 20000229
Last Updated on STN: 20020420
Entered Medline: 20000214

AB In this study we describe the identification and structure-function analysis of a novel death-associated protein (DAP) **kinase**-related protein, DRP-1. DRP-1 is a 42-kDa Ca(2+)/**calmodulin** (CaM)-regulated **serine threonine kinase** which shows high degree of homology to DAP **kinase**. The region of homology spans the catalytic **domain** and the CaM-regulatory region, whereas the remaining **C-terminal** part of the protein differs completely from DAP **kinase** and displays no homology to any known protein. The catalytic **domain** is also homologous to the recently identified ZIP **kinase** and to a lesser extent to the catalytic **domains** of DRAK1 and -2. Thus, DAP **kinase** DRP-1, ZIP **kinase**, and DRAK1/2 together form a novel subfamily of **serine/threonine kinases**.
DRP-1 is localized to the cytoplasm, as shown by immunostaining and cellular fractionation assays. It binds to CaM, undergoes autophosphorylation, and phosphorylates an exogenous substrate, the myosin light chain, in a Ca(2+)/CaM-dependent manner. The truncated protein, deleted of the CaM-regulatory **domain**, was converted into a constitutively active **kinase**. Ectopically expressed DRP-1 induced **apoptosis** in various types of cells. Cell killing by DRP-1 was dependent on two features: the status of the catalytic activity, and the presence of the **C-terminal** 40 amino acids shown to be required for self-dimerization of the **kinase**. Interestingly, further deletion of the CaM-regulatory region could override the indispensable role of the **C-terminal** tail in **apoptosis** and generated a "superkiller" mutant. A dominant negative fragment of DAP **kinase** encompassing the **death domain** was found to block **apoptosis** induced by DRP-1. Conversely, a catalytically inactive mutant of DRP-1, which functioned in a dominant negative manner, was significantly less effective in blocking **cell death** induced by DAP **kinase**. Possible functional connections between DAP **kinase** and DRP-1 are discussed.

=> d his

(FILE 'HOME' ENTERED AT 13:40:52 ON 05 JUN 2002)

FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS, LIFESCI' ENTERED AT 13:41:17 ON 05 JUN 2002
L1 0 S CALMODULAIN

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L2       110146 S CALMODULIN
L3       342878 S SERINE OR THREONINE
L4        73725 S L3 AND KINASE
L5         6021 S L2 AND L4
L6       422053 S (CELL (A) DEATH) OR APOPTOSIS
L7          391 S L5 AND L6
L8          195 S HUMAN AND L7
L9      1023024 S DOMAIN?
L10         111 S L7 AND L9
L11         345 S DAP(A)KINASE?
L12          72 S L10 AND L11
L13          23 DUP REM L12 (49 DUPLICATES REMOVED)
L14      255022 S CARBOXY(W) TERMINAL OR CARBOXY (W)END OR C-TERMINAL
L15          34 S L10 AND L14
L16          17 DUP REM L15 (17 DUPLICATES REMOVED)
L17       10019 S "DAP"
L18           6 S L16 AND L17
L19        4269 S "ZIP"
L20           2 S L16 AND L19
L21          98 S "DRP-1"
L22           1 S L16 AND L21
                E KIMCHI A/AU
L23         484 S E3
L24           3 S L16 AND L23
L25           3 DUP REM L24 (0 DUPLICATES REMOVED)
L26           1 S L25 AND DRP##
L27           7 S L23 AND DRP##
L28           2 DUP REM L27 (5 DUPLICATES REMOVED)
L29          81 S L23 AND L17
L30          18 S L29 AND L14
L31           6 DUP REM L30 (12 DUPLICATES REMOVED)
L32          15 S  L16 AND REGULAT?
L33          15 DUP REM L32 (0 DUPLICATES REMOVED)
L34        3919 S "DEATH DOMAIN?"
L35          19 S L15 AND L34
L36           5 DUP REM L35 (14 DUPLICATES REMOVED)

=> s "dominant negative"
L37       43518 "DOMINANT NEGATIVE"

=> s l16 and l37
L38           5 L16 AND L37

=> d 1-5 ibib ab

L38  ANSWER 1 OF 5     MEDLINE
ACCESSION NUMBER:   2000187596     MEDLINE
DOCUMENT NUMBER:    20187596   PubMed ID: 10722720
TITLE:              Activation of MST/Krs and c-Jun N-terminal kinases
                    by different signaling pathways during cytotrienin
                    A-induced apoptosis.
AUTHOR:             Watabe M; Kakeya H; Onose R; Osada H
CORPORATE SOURCE:   Antibiotics Laboratory, RIKEN, 2-1 Hirosawa, Wako-shi,
                    Saitama 351-0198, Japan.
SOURCE:             JOURNAL OF BIOLOGICAL CHEMISTRY, (2000 Mar 24) 275 (12)
                    8766-71.
                    Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY:       United States
                    Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       Priority Journals
ENTRY MONTH:        200004
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ENTRY DATE: Entered STN: 20000505
Last Updated on STN: 20020420
Entered Medline: 20000427

AB We found that antitumor drugs such as cytotrienin A, camptothecin, taxol, and 5-fluorouracil induced the activation of a 36-kDa protein **kinase** (p36 myelin basic protein (MBP) **kinase**) during **apoptosis** in human promyelocytic leukemia HL-60 cells. This p36 MBP **kinase**, which phosphorylates MBP in an in-gel **kinase** assay, results from the caspase-3-mediated proteolytic cleavage of MST/Krs protein, a mammalian Ste20-like **serine/threonine** **kinase**. Herein the correlation between cytotrienin A-induced **apoptosis** and the activation of MST/Krs proteins was examined in human tumor cell lines, including leukemia-, lung-, epidermoid-, cervix-, stomach-, and brain-derived cell lines. In cytotrienin A-sensitive cell lines, we observed a strong activation of p36 MBP **kinase** by cleavage of the **C-terminal** regulatory **domain** of full-length MST/Krs proteins by caspase-3. When the **kinase** -inactive mutant form of MST/Krs protein was overexpressed in cytotrienin A-sensitive HL-60 cells, the cytotrienin A-induced **apoptosis** was partially inhibited. Because cytotrienin A also activated c-Jun N-terminal **kinase**, we examined the effect of the expression of **dominant negative** c-Jun on cytotrienin A-induced **apoptosis**. The expression of **dominant negative** c-Jun also partially inhibited cytotrienin A-induced **apoptosis**. Furthermore, coexpression of **kinase**-inactive MST/Krs protein and **dominant negative** c-Jun completely suppressed cytotrienin A-induced **apoptosis**. These findings suggest that the proteolytic activation of MST/Krs and c-Jun N-terminal **kinase** activation are involved in cytotrienin A-induced **apoptosis** in human tumor cell lines.

L38 ANSWER 2 OF 5 MEDLINE
ACCESSION NUMBER: 2000144081 MEDLINE
DOCUMENT NUMBER: 20144081 PubMed ID: 10677501
TITLE: A functional genetic screen identifies regions at the **C-terminal** tail and death-**domain** of death-associated protein **kinase** that are critical for its proapoptotic activity.
AUTHOR: Raveh T; Berissi H; Eisenstein M; Spivak T; Kimchi A
CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel.
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (2000 Feb 15) 97 (4) 1572-7. Journal code: PV3; 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200003
ENTRY DATE: Entered STN: 20000330
Last Updated on STN: 20000330
Entered Medline: 20000323

AB Death-associated protein **kinase** (DAP-**kinase**) is a Ca(+2)/**calmodulin**-regulated **serine/threonine** **kinase** with a multidomain structure that participates in **apoptosis** induced by a variety of signals. To identify regions in this protein that are critical for its proapoptotic activity, we performed a genetic screen on the basis of functional selection of short DAP-**kinase**-derived fragments that could protect cells from **apoptosis** by acting in a **dominant-negative** manner. We expressed a library of randomly fragmented DAP-**kinase** cDNA in HeLa cells and treated these cells with IFN-gamma to induce

apoptosis. Functional cDNA fragments were recovered from cells that survived the selection, and those in the sense orientation were examined further in a secondary screen for their ability to protect cells from DAP-**kinase**-dependent tumor necrosis factor-alpha-induced **apoptosis**. We isolated four biologically active peptides that mapped to the ankyrin repeats, the "linker" region, the death **domain**, and the **C-terminal** tail of DAP-**kinase**. Molecular modeling of the complete death **domain** provided a structural basis for the function of the death-**domain** -derived fragment by suggesting that the protective fragment constitutes a distinct substructure. The last fragment, spanning the **C-terminal serine**-rich tail, defined a new regulatory region. Ectopic expression of the tail peptide (17 amino acids) inhibited the function of DAP-**kinase**, whereas removal of this region from the complete protein caused enhancement of the killing activity, indicating that the **C-terminal** tail normally plays a negative regulatory role. Altogether, this unbiased screen highlighted functionally important regions in the protein and revealed an additional level of regulation of DAP-**kinase** apoptotic function that does not affect the catalytic activity.

L38 ANSWER 3 OF 5 MEDLINE
ACCESSION NUMBER: 2000094983 MEDLINE
DOCUMENT NUMBER: 20094983 PubMed ID: 10629061
TITLE: Death-associated protein **kinase**-related protein 1, a novel **serine/threonine kinase** involved in **apoptosis**.
AUTHOR: Inbal B; Shani G; Cohen O; Kissil J L; Kimchi A
CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel.
SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (2000 Feb) 20 (3) 1044-54. Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 20000229
Last Updated on STN: 20020420
Entered Medline: 20000214

AB In this study we describe the identification and structure-function analysis of a novel death-associated protein (DAP) **kinase** -related protein, DRP-1. DRP-1 is a 42-kDa Ca(2+)/**calmodulin** (CaM)-regulated **serine threonine kinase** which shows high degree of homology to DAP **kinase**. The region of homology spans the catalytic **domain** and the CaM-regulatory region, whereas the remaining **C-terminal** part of the protein differs completely from DAP **kinase** and displays no homology to any known protein. The catalytic **domain** is also homologous to the recently identified ZIP **kinase** and to a lesser extent to the catalytic **domains** of DRAK1 and -2. Thus, DAP **kinase** DRP-1, ZIP **kinase**, and DRAK1/2 together form a novel subfamily of **serine/threonine kinases**.
DRP-1 is localized to the cytoplasm, as shown by immunostaining and cellular fractionation assays. It binds to CaM, undergoes autophosphorylation, and phosphorylates an exogenous substrate, the myosin light chain, in a Ca(2+)/CaM-dependent manner. The truncated protein, deleted of the CaM-regulatory **domain**, was converted into a constitutively active **kinase**. Ectopically expressed DRP-1 induced **apoptosis** in various types of cells. Cell killing by DRP-1 was dependent on two features: the status of the catalytic activity, and the presence of the **C-terminal** 40 amino acids

shown to be required for self-dimerization of the **kinase**. Interestingly, further deletion of the CaM-regulatory region could override the indispensable role of the **C-terminal** tail in **apoptosis** and generated a "superkiller" mutant. A **dominant negative** fragment of DAP **kinase** encompassing the death **domain** was found to block **apoptosis** induced by DRP-1. Conversely, a catalytically inactive mutant of DRP-1, which functioned in a **dominant negative** manner, was significantly less effective in blocking **cell death** induced by DAP **kinase**. Possible functional connections between DAP **kinase** and DRP-1 are discussed.

L38 ANSWER 4 OF 5 MEDLINE
ACCESSION NUMBER: 1999430101 MEDLINE
DOCUMENT NUMBER: 99430101 PubMed ID: 10498871
TITLE: Requirement of protein **kinase** (Krs/MST) activation for MT-21-induced **apoptosis**.
AUTHOR: Watabe M; Kakeya H; Osada H
CORPORATE SOURCE: Laboratory of Antibiotics, The Institute of Physical and Chemical Research (RIKEN), 2-1 Hirosawa, Wako, Saitama 351-0198, Japan.
SOURCE: ONCOGENE, (1999 Sep 16) 18 (37) 5211-20. Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY: ENGLAND: United Kingdom Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199910
ENTRY DATE: Entered STN: 19991101 Last Updated on STN: 20020420 Entered Medline: 19991021

AB Fas is a well characterized **apoptosis**-inducing factor. One of our synthetic compounds, MT-21, induced **apoptosis** in human leukemia HL-60 cells similar to Fas. MT-21 activated caspase-3, an important cysteine aspartic protease for **apoptosis** induction. MT-21 also activated c-Jun-NH2-terminal **kinase** (JNK), a member of mitogen activated protein **kinase** (MAPK) superfamily that is involved in the regulation of cell growth, differentiation and **cell death**. Moreover, MT-21 treatment resulted in the activation of a 36 kDa **kinase** which uses myelin basic protein (MBP) as a substrate. However, MAPK and p38 were not activated by treatment with MT-21. The 36 kDa MBP **kinase** was shown to be a proteolytic product derived from the Krs protein with a molecular weight of 60 kDa. The Krs protein is a Ser/Thr protein **kinase** whose activity is enhanced by digestion of its **C-terminal** regulatory **domain** by caspase-3. When a **kinase**-inactive mutant form of Krs protein was overexpressed in HL-60 cells, JNK activation and **apoptosis** induction by MT-21 were suppressed. Furthermore, overexpression of **dominant negative** c-Jun also suppressed **apoptosis** induction by MT-21. These findings indicate that MT-21 induces **apoptosis** by the activation of JNK via the Krs protein, which is activated by caspase cleavage.

L38 ANSWER 5 OF 5 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 2002:89428 SCISEARCH
THE GENUINE ARTICLE: 513UP
TITLE: DAP **kinase** activity is critical for C-2-ceramide-induced **apoptosis** in PC12 cells
AUTHOR: Yamamoto M (Reprint); Hioki T; Ishii T; Nakajima-Iijima S; Uchino S
CORPORATE SOURCE: Mitsubishi Tokyo Pharmaceut Inc, Yokohama Res Ctr, Pharmaceut Discovery Lab, Aoba Ku, 1000 Kamoshida,

Yokohama, Kanagawa 2278502, Japan (Reprint); Mitsubishi Tokyo Pharmaceut Inc, Yokohama Res Ctr, Pharmaceut Discovery Lab, Aoba Ku, Yokohama, Kanagawa 2278502, Japan
COUNTRY OF AUTHOR: Japan
SOURCE: EUROPEAN JOURNAL OF BIOCHEMISTRY, (JAN 2002) Vol. 269, No. 1, pp. 139-147.
Publisher: BLACKWELL SCIENCE LTD, P O BOX 88, OSNEY MEAD, OXFORD OX2 0NE, OXON, ENGLAND.
ISSN: 0014-2956.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 41
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Exposure of PC12 cells to C-2-ceramide results in dose-dependent **apoptosis**. Here, we investigate the involvement of death-associated protein (DAP) **kinase**, initially identified as a positive mediator of the interferon-gamma-induced **apoptosis** of HeLa cells, in the C-2-ceramide-induced **apoptosis** of PC 12 cells. DAP **kinase** is endogenously expressed in these cells. On exposure of PC 12 cells to 30 muM C-2-ceramide, both the total (assayed in the presence of Ca2+/**calmodulin**) and Ca2+/**calmodulin** -independent (assayed in the presence of EGTA) DAP **kinase** activities were transiently increased 5.0- and 12.2-fold, respectively, at 10 min, and then decreased to 1.7- and 3.4-fold at 90 min. After 10 min exposure to 30 mum C-2-ceramide, the Ca2+/**calmodulin** independent activity/total activity ratio increased from 0.22 to 0.60. These effects were dependent on the C-2-ceramide concentration. C-8-ceramide, another active ceramide analog, also induced **apoptosis** and activated DAP **kinase**, while C-2-dihydroceramide, an inactive ceramide analog, failed to induce **apoptosis** and increase DAP **kinase** activity. Furthermore, transfection studies revealed that overexpression of wild-type DAP **kinase** enhanced the sensitivity to C-2- and C-8-ceramide, while a catalytically inactive DAP **kinase** mutant and a construct containing the death **domain** and **C-terminal** tail of DAP **kinase**, which act in a **dominant-negative** manner, rescued cells from C-2-, and C-8-ceramide-induced **apoptosis**. These findings demonstrate that DAP **kinase** is an important component of the apoptotic machinery involved in ceramide-induced **apoptosis**, and that the intrinsic DAP **kinase** activity is critical for ceramide-induced **apoptosis**.

=> d his

(FILE 'HOME' ENTERED AT 13:40:52 ON 05 JUN 2002)

FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS, LIFESCI' ENTERED AT 13:41:17 ON 05 JUN 2002

L1	0	S	CALMODULAIN
L2	110146	S	CALMODULIN
L3	342878	S	SERINE OR THREONINE
L4	73725	S	L3 AND KINASE
L5	6021	S	L2 AND L4
L6	422053	S	(CELL (A) DEATH) OR APOPTOSIS
L7	391	S	L5 AND L6
L8	195	S	HUMAN AND L7
L9	1023024	S	DOMAIN?
L10	111	S	L7 AND L9
L11	345	S	DAP(A)KINASE?
L12	72	S	L10 AND L11
L13	23	DUP REM	L12 (49 DUPLICATES REMOVED)

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L14       255022 S CARBOXY(W) TERMINAL OR CARBOXY (W)END OR C-TERMINAL
L15           34 S L10 AND L14
L16           17 DUP REM L15 (17 DUPLICATES REMOVED)
L17        10019 S "DAP"
L18            6 S L16 AND L17
L19         4269 S "ZIP"
L20            2 S L16 AND L19
L21           98 S "DRP-1"
L22            1 S L16 AND L21
                 E KIMCHI A/AU
L23          484 S E3
L24            3 S L16 AND L23
L25            3 DUP REM L24 (0 DUPLICATES REMOVED)
L26            1 S L25 AND DRP##
L27            7 S L23 AND DRP##
L28            2 DUP REM L27 (5 DUPLICATES REMOVED)
L29           81 S L23 AND L17
L30           18 S L29 AND L14
L31            6 DUP REM L30 (12 DUPLICATES REMOVED)
L32           15 S  L16 AND REGULAT?
L33           15 DUP REM L32 (0 DUPLICATES REMOVED)
L34         3919 S "DEATH DOMAIN?"
L35           19 S L15 AND L34
L36            5 DUP REM L35 (14 DUPLICATES REMOVED)
L37        43518 S "DOMINANT NEGATIVE"
L38            5 S L16 AND L37

=>
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1	L1	22744	kinase$2
2	L2	1802	calmodulin
3	L3	506	l1 same l2
4	L4	9798	(cell adj death) or apoptosis
5	L5	11	l3 same l4
6	L6	2	DAP adj kinase?
7	L7	0	"drp-1"
8	L8	18156	"carboxy terminal" or "c-terminal" or "carboxy end"
9	L9	38	l3 same l8
10	L10	1	l4 same l9
11	L11	20	kimchi.in.
12	L12	2	l3 and l11

	Document ID △	Issue Date	Title
1	US 20010051335 A1	20011213	POLYNUCLEOTIDES AND POLYPEPTIDES DERIVED FROM CORN TASSEL
2	US 20020039734 A1	20020404	Compositions, kits, and methods for identification and modulation of T helper-1 and T helper-2 cells and diseases associated therewith
3	US 20020039764 A1	20020404	Nucleic, acids, proteins, and antibodies
4	US 20020040489 A1	20020404	Expressed sequences of arabidopsis thaliana
5	US 20020055627 A1	20020509	Nucleic acids, proteins and antibodies
6	US 5968816 A	19991019	Tumor suppressor genes, proteins encoded thereby and use of said genes and proteins
7	US 6025194 A	20000215	Nucleic acid sequence of senescence asssociated gene
8	US 6090554 A	20000718	Efficient construction of gene targeting vectors
9	US 6090629 A	20000718	Efficient construction of gene targeting using phage-plasmid recombination
10	US 6160106 A	20001212	Tumor suppressor genes, proteins encoded thereby and use of said genes and proteins
11	US 6221647 B1	20010424	Efficient construction of gene targeting using phage-plasmid recombination

	U	1	Pages	Document ID △	Issue Date
1	☒	☐	24	US 5958748 A	19990928
2	☒	☐	24	US 6171841 B1	20010109

	Title	Current OR	Current XRef
1	DNA coding for serine/threonine kinase	435/194	435/252.1; 435/320.1; 435/325
2	DNA coding for serine/threonine kinase	435/194	435/252.33; 435/254.11; 435/320.1; 536/23.1; 536/23.2; 536/23.5

	Retrieval Classif	Inventor	S	C	P	2	3	4	5
1		Akira, Shizuo et al.	☐	☐	☐	☐	☐	☐	☐
2		Akira, Shizuo et al.	☐	☐	☐	☐	☐	☐	☐

	Image Doc. Displayed	PT
1	US 5958748	☐
2	US 6171841	☐

	Document ID △	Issue Date
1	US 20010051335 A1	20011213

	Document ID △	Issue Date	Title
1	US 5968816 A	19991019	Tumor suppressor genes, proteins encoded thereby and use of said genes and proteins
2	US 6160106 A	20001212	Tumor suppressor genes, proteins encoded thereby and use of said genes and proteins